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(71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(74) Agents: MAGATTI, Anita, W. et al.; Schering-Plough Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		
(72) Inventors; and (75) Inventors/Applicants (for US only): BAROUDY, Bahige, M. [US/US]; 706 Central Avenue, Westfield, NJ 07090 (US). CLADER, John, W. [US/US]; 428 North Union Avenue, Cranford, NJ 07016 (US). JOSIEN, Hubert, B. [FR/US]; 5441 Washington Boulevard, Jersey City, NJ 07310 (US). McCOMBIE, Stuart, W. [GB/US]; 28 Hanford Place, Caldwell, NJ 07006 (US). McKITTRICK, Brian, A. [US/US];		(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).		
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(54) Title: PIPERIDINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS				
(57) Abstract <p>The use of CCR5 antagonists of formula (I) or a pharmaceutically acceptable salt thereof, wherein X is $-\text{C}(\text{R}^{13})_2-$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}(\text{alkyl})-$, (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m) or (n); R is optionally substituted phenyl, pyridyl, thiophenyl or naphthyl; R¹ is H, alkyl or alkenyl; R² is optionally substituted phenyl, phenylalkyl, heteroaryl or heteroarylalkyl, naphthyl, fluorenyl or diphenylmethyl; R³ is optionally substituted phenyl, heteroaryl or naphthyl; R⁴ is H, alkyl, fluoro-alkyl, cyclopropylmethyl, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2-\text{O}-\text{alkyl}$, $-\text{CH}_2\text{C}(\text{O})-\text{O}-\text{alkyl}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})-\text{NHalkyl}$ or $-\text{CH}_2\text{C}(\text{O})-\text{N}(\text{alkyl})_2$; R¹⁹ is optionally substituted phenyl, heteroaryl or naphthyl, cycloalkyl, cycloalkylalkyl or alkoxyalkyl; and R⁵, R¹³, R¹⁴, R¹⁵ and R¹⁶ are hydrogen or alkyl for the treatment of HIV, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis is disclosed, as well as novel compounds, pharmaceutical compositions comprising them, and the combination of CCR5 antagonists of the invention in combination with antiviral agents useful in the treatment of HIV or agents useful in the treatment of inflammatory diseases.</p>				

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PIPERIDINE DERIVATIVES USEFUL AS CCR5 ANTAGONISTS

10 BACKGROUND

The present invention relates to piperidine derivatives useful as selective CCR5 antagonists, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds. The invention also relates to the use of a combination of a CCR5 antagonist of 15 this invention and one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus (HIV). The invention further relates to the use of a CCR-5 antagonist of this invention, alone or in combination with another agent, in the treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory 20 bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis.

The global health crisis caused by HIV, the causative agent of Acquired Immunodeficiency Syndrome (AIDS), is unquestioned, and while recent advances in drug therapies have been successful in slowing the 25 progression of AIDS, there is still a need to find a safer, more efficient, less expensive way to control the virus.

It has been reported that the CCR5 gene plays a role in resistance to HIV infection. HIV infection begins by attachment of the virus to a target cell membrane through interaction with the cellular receptor CD4 and a 30 secondary chemokine co-receptor molecule, and proceeds by replication and dissemination of infected cells through the blood and other tissue. There are various chemokine receptors, but for macrophage-tropic HIV, believed to be the key pathogenic strain that replicates *in vivo* in the early stages of infection, the principal chemokine receptor required for the entry 35 of HIV into the cell is CCR5. Therefore, interfering with the interaction between the viral receptor CCR5 and HIV can block HIV entry into the cell. The present invention relates to small molecules which are CCR5 antagonists.

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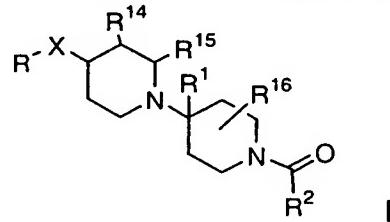
CCR-5 receptors have been reported to mediate cell transfer in inflammatory diseases such as arthritis, rheumatoid arthritis, atopic dermatitis, psoriasis, asthma and allergies, and inhibitors of such receptors are expected to be useful in the treatment of such diseases, and in the
 5 treatment of other inflammatory diseases or conditions such as inflammatory bowel disease, multiple sclerosis, solid organ transplant rejection and graft v. host disease.

Related piperidine derivatives which are muscarinic antagonists useful in the treatment of cognitive disorders such as Alzheimer's disease
 10 are disclosed in US patents 5,883,096; 6,037,352; 5,889,006; 5,952,349; and 5,977,138.

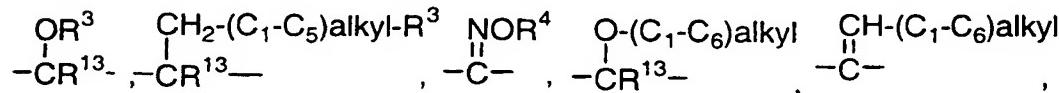
A-M. Vandamme et al., *Antiviral Chemistry & Chemotherapy*, 9:187-203 (1998) disclose current clinical treatments of HIV-1 infections in man including at least triple drug combinations or so-called Highly Active
 15 Antiretroviral Therapy ("HAART"); HAART involves various combinations of nucleoside reverse transcriptase inhibitors ("NRTI"), non-nucleoside reverse transcriptase inhibitors ("NNRTI") and HIV protease inhibitors ("PI"). In compliant drug-naive patients, HAART is effective in reducing mortality and progression of HIV-1 to AIDS. However, these multidrug therapies do
 20 not eliminate HIV-1 and long-term treatment usually results in multidrug resistance. Development of new drug therapies to provide better HIV-1 treatment remains a priority.

SUMMARY OF THE INVENTION

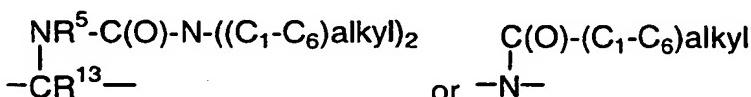
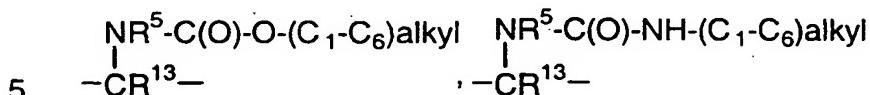
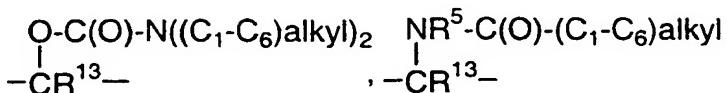
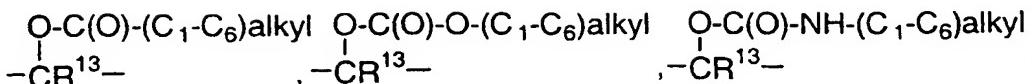
25 The present invention relates to the treatment of HIV comprising administering to a human in need of such treatment an effective amount of a CCR5 antagonist represented by the structural formula I:



or a pharmaceutically acceptable salt thereof, wherein
 30 X is -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,



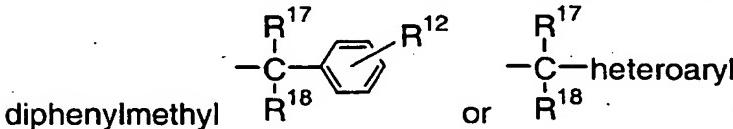
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R is R⁶-phenyl, R⁶-pyridyl, R⁶-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

10 R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide; R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl;

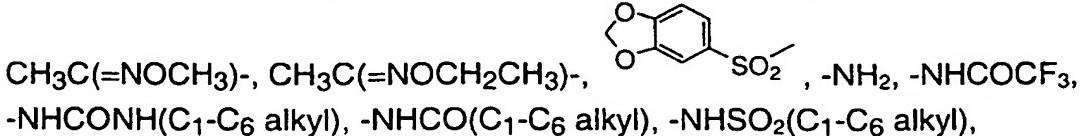


R³ is R⁶-phenyl, R⁶-heteroaryl or R⁶-naphthyl;

15 R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

20 R⁶ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-, CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl,



25 5-membered heteroaryl and $\begin{array}{c} \text{O} \\ || \\ \text{N}-\text{X} \end{array}$, wherein X is -O-, -NH- or -N(CH₃)-; R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO,

-CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl,

30 -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-

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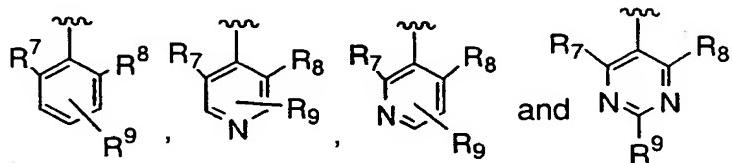
- cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆)alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R²⁰R²¹, -CON(CH₂CH₂-O-
- 5 CH₃)₂,
- OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;
- R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;
- R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R₂₀, -CN, (C₁-C₆)alkoxy and halogen;
- 10 R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;
- R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene
- 15 group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;
- R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C₃-C₁₀ cycloalkyl, (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl or (C₁-C₆)alkoxy(C₁-C₆)alkyl;
- R²⁰, R²¹ and R²² are independently selected from the group
- 20 consisting of H and C₁-C₆ alkyl; and
- R²³ is C₁-C₆ alkyl or phenyl.

Preferred are compounds of formula I wherein R is R⁶-phenyl, especially wherein R⁶ is a single substituent, and especially wherein the R⁶ substituent is in the 4-position. Also preferred are compounds of formula I wherein R¹³, R¹⁴, R¹⁵ and R¹⁶ are each hydrogen or methyl, especially hydrogen. Also preferred are compounds of formula I wherein X is -CHOR³, -C(R¹³)(R¹⁹)- or -C(=NOR⁴)-; a preferred definition for R³ is pyridyl, especially 2-pyridyl, a preferred definition for R⁴ is (C₁-C₆)alkyl, especially methyl, ethyl or isopropyl, a preferred definition for R¹³ is hydrogen, and a preferred definition for R¹⁹ is R⁶-phenyl. For compounds of formula I, R¹ is preferably (C₁-C₆)alkyl, especially methyl.

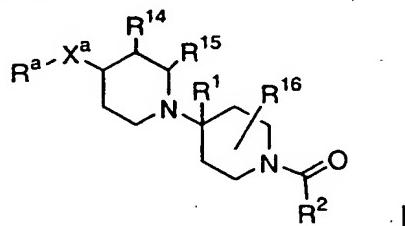
In compounds of formula I, R² is preferably R⁷, R⁸, R⁹-phenyl, R⁷, R⁸, R⁹-pyridyl or an N-oxide thereof, or R⁷, R⁸, R⁹-pyrimidyl. When R² is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R⁷ and R⁸ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R⁹ substituent can be attached to any of the remaining

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unsubstituted carbon ring members, for example as shown in the following structures:



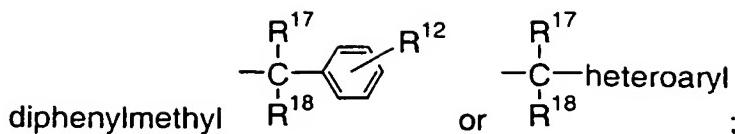
- Preferred R⁷ and R⁸ substituents are: (C₁-C₆)alkyl, especially methyl; halogen, especially chloro; and -NH₂. A preferred R⁹ substituent is hydrogen.
- 5 Also claimed are novel CCR5 antagonist compounds represented by the structural formula II



- 10 or a pharmaceutically acceptable salt thereof, wherein
- (1) X^a is -C(R¹³)₂-, -C(R¹³)(R¹⁹)-, -C(O)-, -O-, -NH-, -N((C₁-C₆)alkyl)-,
- OR³ CH₂-(C₁-C₅)alkyl-R³ NOR⁴ O-(C₁-C₆)alkyl CH-(C₁-C₆)alkyl
 -CR¹³- , -CR¹³- , -C- , -CR¹³- , -C- ,
- O-C(O)-(C₁-C₆)alkyl O-C(O)-O-(C₁-C₆)alkyl O-C(O)-NH-(C₁-C₆)alkyl
 -CR¹³- , -CR¹³- , -CR¹³- ,
- O-C(O)-N((C₁-C₆)alkyl)₂ NR⁵-C(O)-(C₁-C₆)alkyl
 -CR¹³- , -CR¹³- ;
- NR⁵-C(O)-O-(C₁-C₆)alkyl NR⁵-C(O)-NH-(C₁-C₆)alkyl
 -CR¹³- , -CR¹³- ;
- NR⁵-C(O)-N-((C₁-C₆)alkyl)₂ C(O)-(C₁-C₆)alkyl
 -CR¹³- or -N- ;

- R^a is R^{6a}-phenyl, R^{6a}-pyridyl, R^{6a}-thiophenyl or R⁶-naphthyl;
- R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;
- R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide;
- 25 R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl;

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R³ is R¹⁰-phenyl, pyridyl, pyrimidyl, pyrazinyl or thiazolyl;

R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl, -CH₂CH₂OH, -CH₂CH₂O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl, -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

5 R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R^{6a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, -CF₃, CF₃O-, -CN, -CF₃SO₂-, R¹²-phenyl,

10 R⁶ is independently selected from the group consisting of R^{6a} and CH₃SO₂-;

10 -NHCOCF₃, 5-membered heteroaryl and , wherein X is -O-, -NH- or -N(CH₃)-;

15 R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

15 R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, -N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)-cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NHSO₂N((C₁-C₆)alkyl)₂, -NHSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀ cycloalkyl, -SR²³, -SOR²³, -SO₂R²³, -SO₂NH(C₁-C₆ alkyl), -OSO₂(C₁-C₆)alkyl, -OSO₂CF₃, hydroxy(C₁-C₆)alkyl, -CON R²⁰R²¹, -CON(CH₂CH₂-O-CH₃)₂, -OCONH(C₁-C₆)alkyl, -CO₂R²⁰, -Si(CH₃)₃ or -B(OC(CH₃)₂)₂;

25 R¹⁰ is (C₁-C₆)alkyl, -NH₂ or R¹²-phenyl;

R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, -CF₃, -CO₂R₂₀, -CN, (C₁-C₆)alkoxy and halogen;

30 R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C₁-C₆)alkyl;

R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C₁-C₆ alkyl, or R¹⁷ and R¹⁸ together are a C₂-C₅ alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

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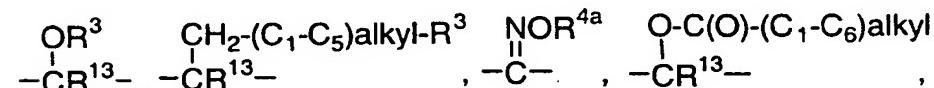
R^{19} is R^6 -phenyl, R^6 -heteroaryl, R^6 -naphthyl, C_3 - C_{10} cycloalkyl, (C_3 - C_{10})cycloalkyl(C_1 - C_6)alkyl or (C_1 - C_6)alkoxy(C_1 - C_6)alkyl;

R^{20} , R^{21} and R^{22} are independently selected from the group consisting of H and C_1 - C_6 alkyl; and

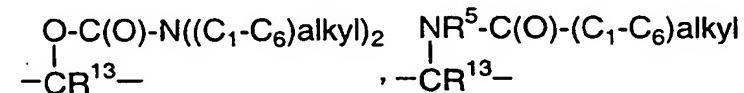
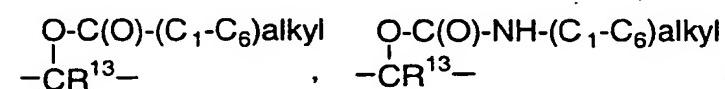
5 R^{23} is C_1 - C_6 alkyl or phenyl; or

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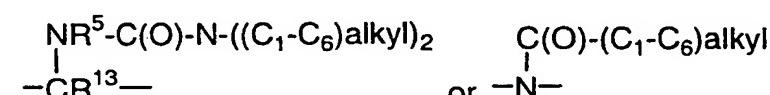
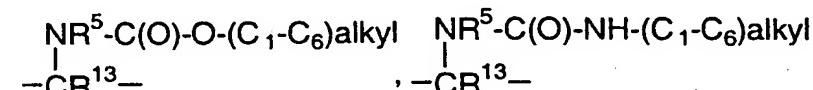
X^a is $-C(R^{13})(R^{19})-$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)alkyl)-$,



10



15



R^a is R^{6b} -phenyl, R^{6b} -pyridyl or R^{6b} -thiophenyl;

R^{4a} is fluoro- C_1 - C_6 alkyl, cyclopropylmethyl, $-CH_2CH_2OH$,

20 $-CH_2CH_2O-(C_1-C_6)alkyl$, $-CH_2C(O)-O-(C_1-C_6)alkyl$, $-CH_2C(O)NH_2$, $-CH_2C(O)-NH-(C_1-C_6)alkyl$ or $-CH_2C(O)-N((C_1-C_6)alkyl)_2$;

R^{6b} is $CH_3SO_2^-$; and

25 R^1 , R^2 , R^3 , R^5 , R^{14} , R^{15} , R^{16} and R^{19} are as defined in (1).

25 Preferred are compounds of formula II(1) wherein R^a is R^{6a} -phenyl, especially wherein R^{6a} is a single substituent, and especially wherein the R^{6a} substituent is in the 4-position. Also preferred are compounds of formula II(1) wherein X^a is $-CHOR^3$, $-C(R^{13})(R^{19})-$ or $-C(=NOR^4)-$; a preferred definition for R^3 is pyridyl, especially 2-pyridyl, a preferred definition for R^4 is (C_1 - C_6)alkyl, especially methyl, ethyl or isopropyl, a preferred definition for R^{13} is hydrogen, and a preferred definition for R^{19} is R^6 -phenyl. For compounds of formula II(1), R^1 is preferably (C_1 - C_6)alkyl,

especially methyl. Also for compounds of formula II(1), R¹⁴, R¹⁵ and R¹⁶ are preferably hydrogen.

- Preferred are compounds of formula II(2) wherein R^a is R^{6b}-phenyl, especially wherein R^{6b} is a single substituent, and especially wherein the R^{6b} substituent is in the 4-position. Also preferred are compounds of formula II(2) wherein X^a is -CHOR³, -C(R¹³)(R¹⁹)- or -C(=NOR^{4a})-; a preferred definition for R³ is pyridyl, especially 2-pyridyl, preferred definitions for R^{4a} are cyclopropylmethyl and trifluoroethyl, a preferred definition for R¹³ is hydrogen, and a preferred definition for R¹⁹ is R⁶-phenyl.
- For compounds of formula II(2), R¹ is preferably (C₁-C₆)alkyl, especially methyl. Also for compounds of formula II(2), R¹⁴, R¹⁵ and R¹⁶ are preferably hydrogen.

- In compounds of formula II(1) and (2), R² is preferably R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-pyridyl or an N-oxide thereof; or R⁷, R⁸, R⁹-pyrimidyl.
- When R² is pyridyl, it is preferably 3- or 4-pyridyl, and when pyrimidyl, it is preferably 5-pyrimidyl. The R⁷ and R⁸ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule and the R⁹ substituent can be attached to any of the remaining unsubstituted carbon ring members as shown above for compounds of formula I. Preferred R⁷ and R⁸ substituents for compounds of formula II are: (C₁-C₆)alkyl, especially methyl; halogen, especially chloro; and -NH₂; a preferred R⁹ substituent is hydrogen.

- Another aspect of the invention is a pharmaceutical composition for treatment of HIV comprising an effective amount of a CCR5 antagonist of formula II in combination with a pharmaceutically acceptable carrier.
- Another aspect of the invention is a pharmaceutical composition for treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis comprising an effective amount of a CCR5 antagonist of formula II in combination with a pharmaceutically acceptable carrier.

- Yet another aspect of this invention is a method of treatment of HIV comprising administering to a human in need of such treatment an effective amount of a CCR5 antagonist compound of formula II. Another aspect of the invention is a method of treatment of solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis

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comprising administering to a human in need of such treatment an effective amount of a CCR5 antagonist compound of formula I or II.

Still another aspect of this invention is the use of a CCR5 antagonist of formula I or II of this invention in combination with one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus for the treatment of AIDS. Still another aspect of this invention is the use of a CCR5 antagonist of formula I or II of this invention in combination with one or more other agents useful in the treatment of solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis. The CCR5 and antiviral or other agents which are components of the combination can be administered in a single dosage form or they can be administered separately; a kit comprising separate dosage forms of the actives is also contemplated.

15 **DETAILED DESCRIPTION OF THE INVENTION**

As used herein, the following terms are used as defined below unless otherwise indicated.

Alkyl (including the alkyl portions of alkoxy, alkylamino and dialkylamino) represents straight and branched carbon chains and contains 20 from one to six carbon atoms.

Alkenyl represents C₂-C₆ carbon chains having one or two unsaturated bonds, provided that two unsaturated bonds are not adjacent to each other.

Substituted phenyl means that the phenyl group can be substituted 25 at any available position on the phenyl ring.

Acyl means a radical of a carboxylic acid having the formula alkyl-C(O)-, aryl-C(O)-, aralkyl-C(O)-, (C₃-C₇)cycloalkyl-C(O)-, (C₃-C₇)cycloalkyl-(C₁-C₆)alkyl-C(O)-, and heteroaryl-C(O)-, wherein alkyl and heteroaryl are as defined herein; aryl is R¹²-phenyl or R¹²-naphthyl; and 30 aralkyl is aryl-(C₁-C₆)alkyl, wherein aryl is as defined above.

Heteroaryl represents cyclic aromatic groups of 5 or 6 atoms or bicyclic groups of 11 to 12 atoms having 1 or 2 heteroatoms independently selected from O, S or N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to 35 provide aromatic character, provided that the rings do not contain adjacent oxygen and/or sulfur atoms. For 6-membered heteroaryl rings, carbon atoms can be substituted by R⁷, R⁸ or R⁹ groups. Nitrogen atoms can form an N-oxide. All regioisomers are contemplated, e.g., 2-pyridyl, 3-

- 10 -

pyridyl and 4-pyridyl. Typical 6-membered heteroaryl groups are pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and the N-oxides thereof. For 5-membered heteroaryl rings, carbon atoms can be substituted by R¹⁰ or R¹¹ groups. Typical 5-membered heteroaryl rings are furyl, thienyl, pyrrolyl, 5 thiazolyl, isothiazolyl, imidazolyl, pyrazolyl and isoxazolyl. 5-Membered rings having one heteroatom can be joined through the 2- or 3- position; 5-membered rings having two heteroatoms are preferably joined through the 4-position. Bicyclic groups typically are benzo-fused ring systems derived from the heteroaryl groups named above, e.g. quinolyl, phthalazinyl, 10 quinazolinyl, benzofuranyl, benzothienyl and indolyl.

Preferred points of substitution for 6-membered heteroaryl rings at R² are described above. When R² is a 5-membered heteroaryl group, the R¹⁰ and R¹¹ substituents are preferably attached to carbon ring members adjacent to the carbon joining the ring to the rest of the molecule, and R¹¹ 15 is preferably alkyl; however, if a heteroatom is adjacent to the carbon joining the ring to the rest of the molecule (i.e., as in 2-pyrrolyl), R¹⁰ is preferably attached to a carbon ring member adjacent to the carbon joining the ring to the rest of the molecule.

Halogen represents fluoro, chloro, bromo and iodo.
20 Fluoro(C₁-C₆)alkyl represents a straight or branched alkyl chain substituted by 1 to 5 fluoro atoms, which can be attached to the same or different carbon atoms, e.g., -CH₂F, -CHF₂, -CF₃, F₃CCH₂- and -CF₂CF₃.

A therapeutically effective amount of a CCR5 antagonist is an amount sufficient to lower HIV-1-RNA plasma levels.
25 One or more, preferably one to four, antiviral agents useful in anti-HIV-1 therapy may be used in combination with a CCR5 antagonist of the present invention. The antiviral agent or agents may be combined with the CCR5 antagonist in a single dosage form, or the CCR5 antagonist and the antiviral agent or agents may be administered simultaneously or 30 sequentially as separate dosage forms. The antiviral agents contemplated for use in combination with the compounds of the present invention comprise nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and other antiviral drugs listed below not falling within these classifications. In 35 particular, the combinations known as HAART are contemplated for use in combination with the CCR5 antagonists of this invention.

The term "nucleoside and nucleotide reverse transcriptase inhibitors" ("NRTI's") as used herein means nucleosides and nucleotides and

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analogues thereof that inhibit the activity of HIV-1 reverse transcriptase, the enzyme which catalyzes the conversion of viral genomic HIV-1 RNA into proviral HIV-1 DNA.

- Typical suitable NRTIs include zidovudine (AZT) available under the
- 5 RETROVIR tradename from Glaxo-Wellcome Inc., Research Triangle, NC 27709; didanosine (ddI) available under the VIDEX tradename from Bristol-Myers Squibb Co., Princeton, NJ 08543; zalcitabine (ddC) available under the Hivid tradename from Roche Pharmaceuticals, Nutley, NJ 07110; stavudine (d4T) available under the ZERIT trademark from Bristol-
- 10 Myers Squibb Co., Princeton, NJ 08543; lamivudine (3TC) available under the EPIVIR tradename from Glaxo-Wellcome Research Triangle, NC 27709; abacavir (1592U89) disclosed in WO96/30025 and available under the ZIAGEN trademark from Glaxo-Wellcome Research Triangle, NC 27709; adefovir dipivoxil [bis(POM)-PMEA] available under the PREVON
- 15 trademark from Gilead Sciences, Foster City, CA 94404; lobucavir (BMS-180194), a nucleoside reverse transcriptase inhibitor disclosed in EP-0358154 and EP-0736533 and under development by Bristol-Myers Squibb, Princeton, NJ 08543; BCH-10652, a reverse transcriptase inhibitor (in the form of a racemic mixture of BCH-10618 and BCH-10619) under
- 20 development by Biochem Pharma, Laval, Quebec H7V, 4A7, Canada; emtricitabine [(-)-FTC] licensed from Emory University under Emory Univ. U.S. Patent No. 5,814,639 and under development by Triangle Pharmaceuticals, Durham, NC 27707; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dideoxy-5-fluoro-cytidine) licensed by Yale
- 25 University to Vion Pharmaceuticals, New Haven CT 06511; DAPD, the purine nucleoside, (-)-beta-D-2,6,-diamino-purine dioxolane disclosed in EP 0656778 and licensed by Emory University and the University of Georgia to Triangle Pharmaceuticals, Durham, NC 27707; and Idenosine (FddA), 9-(2,3-dideoxy-2-fluoro- β -D-threo-pentofuranosyl)adenine, an acid stable
- 30 purine-based reverse transcriptase inhibitor discovered by the NIH and under development by U.S. Bioscience Inc., West Conshohoken, PA 19428.

The term "non-nucleoside reverse transcriptase inhibitors" ("NNRTI's) as used herein means non-nucleosides that inhibit the activity of HIV-1 reverse transcriptase.

Typical suitable NNRTIs include nevirapine (BI-RG-587) available under the VIRAMUNE tradename from Boehringer Ingelheim, the manufacturer for Roxane Laboratories, Columbus, OH 43216; delavirdine

(BHAP, U-90152) available under the RESRIPTOR tradename from Pharmacia & Upjohn Co., Bridgewater NJ 08807; efavirenz (DMP-266) a benzoxazin-2-one disclosed in WO94/03440 and available under the SUSTIVA tradename from DuPont Pharmaceutical Co., Wilmington, DE

5 19880-0723; PNU-142721, a furopyridine-thio-pyrimide under development by Pharmacia and Upjohn, Bridgewater NJ 08807; AG-1549 (formerly Shionogi # S-1153); 5-(3,5-dichlorophenyl)- thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbonate disclosed in WO 96 /10019 and under clinical development by Agouron Pharmaceuticals, Inc., LaJolla

10 10 CA 92037-1020; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione) discovered by Mitsubishi Chemical Co. and under development by Triangle Pharmaceuticals, Durham, NC 27707; and (+)-calanolide A (NSC-675451) and B, coumarin derivatives disclosed in NIH U.S. Patent No. 5,489,697, licensed to Med

15 15 Chem Research, which is co-developing (+) calanolide A with Vita-Invest as an orally administrable product.

The term "protease inhibitor" ("PI") as used herein means inhibitors of the HIV-1 protease, an enzyme required for the proteolytic cleavage of viral polyprotein precursors (e.g., viral GAG and GAG Pol polyproteins),

20 20 into the individual functional proteins found in infectious HIV-1. HIV protease inhibitors include compounds having a peptidomimetic structure, high molecular weight (7600 daltons) and substantial peptide character, e.g. CRIXIVAN(available from Merck) as well as nonpeptide protease inhibitors e.g., VIRACEPT (available from Agouron).

25 25 Typical suitable PIs include saquinavir (Ro 31-8959) available in hard gel capsules under the INVIRASE tradename and as soft gel capsules under the FORTOVASE tradename from Roche Pharmaceuticals, Nutley, NJ 07110-1199; ritonavir (ABT-538) available under the NORVIR tradename from Abbott Laboratories, Abbott Park, IL 60064; indinavir (MK-30 30 639) available under the CRIXIVAN tradename from Merck & Co., Inc., West Point, PA 19486-0004; nelfnavir (AG-1343) available under the VIRACEPT tradename from Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020; amprenavir (141W94), tradename AGENERASE, a non-peptide protease inhibitor under development by Vertex Pharmaceuticals, Inc., Cambridge, MA 02139-4211 and available from Glaxo-Wellcome, Research Triangle, NC under an expanded access program; lasinavir (BMS-234475) available from Bristol-Myers Squibb, Princeton, NJ 08543 (originally discovered by Novartis, Basel, Switzerland (CGP-61755); DMP-

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450, a cyclic urea discovered by Dupont and under development by Triangle Pharmaceuticals; BMS-2322623, an azapeptide under development by Bristol-Myers Squibb, Princeton, NJ 08543, as a 2nd-generation HIV-1 PI; ABT-378 under development by Abbott , Abbott Park,
5 IL 60064; and AG-1549 an orally active imidazole carbamate discovered by Shionogi (Shionogi #S-1153) and under development by Agouron Pharmaceuticals, Inc., LaJolla CA 92037-1020.

Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No. 11607. Hydroxyurea (Droxia), a
10 ribonucleoside triphosphate reductase inhibitor, the enzyme involved in the activation of T-cells, was discovered at the NCI and is under development by Bristol-Myers Squibb; in preclinical studies, it was shown to have a synergistic effect on the activity of didanosine and has been studied with stavudine. IL-2 is disclosed in Ajinomoto EP-0142268 , Takeda EP-
15 0176299, and Chiron U. S. Patent Nos. RE 33653, 4530787, 4569790, 4604377, 4748234, 4752585, and 4949314, and is available under the PROLEUKIN (aldesleukin) tradename from Chiron Corp., Emeryville, CA 94608-2997 as a lyophilized powder for IV infusion or sc administration upon reconstitution and dilution with water; a dose of about 1 to about 20
20 million IU/day, sc is preferred; a dose of about 15 million IU/day, sc is more preferred. IL-12 is disclosed in WO96/25171 and is available from Roche Pharmaceuticals, Nutley, NJ 07110-1199 and American Home Products, Madison, NJ 07940; a dose of about 0.5 microgram/kg/day to about 10 microgram/kg/day, sc is preferred. Pentafuside (DP-178, T-20) a 36-amino
25 acid synthetic peptide, disclosed in U.S. Patent No.5,464,933 licensed from Duke University to Trimeris which is developing pentafuside in collaboration with Duke University; pentafuside acts by inhibiting fusion of HIV-1 to target membranes. Pentafuside (3-100 mg /day) is given as a continuous sc infusion or injection together with efavirenz and 2 PI's to HIV-1 positive
30 patients refractory to a triple combination therapy; use of 100 mg/day is preferred. Yissum Project No. 11607, a synthetic protein based on the HIV -1 Vif protein, is under preclinical development by Yissum Research Development Co., Jerusalem 91042 , Israel. Ribavirin, 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, is available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; its manufacture and formulation are described in U.S. Patent No. 4,211,771.

The term "anti-HIV-1 therapy" as used herein means any anti-HIV-1 drug found useful for treating HIV-1 infections in man alone, or as part of

multidrug combination therapies, especially the HAART triple and quadruple combination therapies. Typical suitable known anti-HIV-1 therapies include, but are not limited to multidrug combination therapies such as (i) at least three anti-HIV-1 drugs selected from two NRTIs, one PI,
5 a second PI, and one NNRTI; and (ii) at least two anti-HIV-1 drugs selected from NNRTIs and PIs. Typical suitable HAART - multidrug combination therapies include:

- (a) triple combination therapies such as two NRTIs and one PI ; or
(b) two NRTIs and one NNRTI ; and (c) quadruple combination therapies
10 such as two NRTIs , one PI and a second PI or one NNRTI. In treatment of naive patients, it is preferred to start anti-HIV-1 treatment with the triple combination therapy; the use of two NRTIs and one PI is prefered unless there is intolerance to PIs. Drug compliance is essential. The CD4⁺ and HIV-1-RNA plasma levels should be monitored every 3-6 months. Should
15 viral load plateau, a fourth drug,e.g., one PI or one NNRTI could be added. See the table below wherein typical therapies are further described:

ANTI-HIV-1 MULTI DRUG COMBINATION THERAPIES

A. Triple Combination Therapies

1. Two NRTIs¹ + one PI²
20 2. Two NRTIs¹ + one NNRTI³

B. Quadruple Combination Therapies⁴

Two NRTIs + one PI + a second PI or one NNRTI

25 C. ALTERNATIVES:⁵

- Two NRTI¹
One NRTI⁵ + one PI²
Two PIs⁶ ± one NRTI⁷ or NNRTI³
One PI² + one NRTI⁷ + one NNRTI³

30 FOOTNOTES TO TABLE

1. One of the following: zidovudine + lamivudine; zidovudine + didanosine; stavudine + lamivudine; stavudine + didanosine; zidovudine + zalcitabine
- 35 2. Indinavir, nelfinavir, ritonavir or saquinavir soft gel capsules.
3. Nevirapine or delavirdine.
4. See A-M. Vandamne et al Antiviral Chemistry & Chemotherapy 9:187 at p 193-197 and Figures 1 + 2.

5. Alternative regimens are for patients unable to take a recommended regimen because of compliance problems or toxicity, and for those who fail or relapse on a recommended regimen. Double nucleoside combinations may lead to HIV-resistance and clinical failure in many patients.
 6. Most data obtained with saquinavir and ritonavir (each 400 mg bid).
 7. Zidovudine, stavudine or didanosine.
- 10 Agents known in the treatment of rheumatoid arthritis, transplant and graft v. host disease, inflammatory bowel disease and multiple sclerosis which can be administered in combination with the CCR5 antagonists of the present invention are as follows:
- solid organ transplant rejection and graft v. host disease: immune suppressants such as cyclosporine and Interleukin-10 (IL-10), tacrolimus, antilymphocyte globulin, OKT-3 antibody, and steroids;
- 15 inflammatory bowel disease: IL-10 (see US 5,368,854), steroids and azulfidine;
- rheumatoid arthritis: methotrexate, azathioprine, cyclophosphamide, 20 steroids and mycophenolate mofetil;
- multiple sclerosis: interferon-beta, interferon-alpha, and steroids.

Certain CCR5 antagonist compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers and atropisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

Certain compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may 30 include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds also form pharmaceutically acceptable 35 salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric,

acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the
5 conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and
10 base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

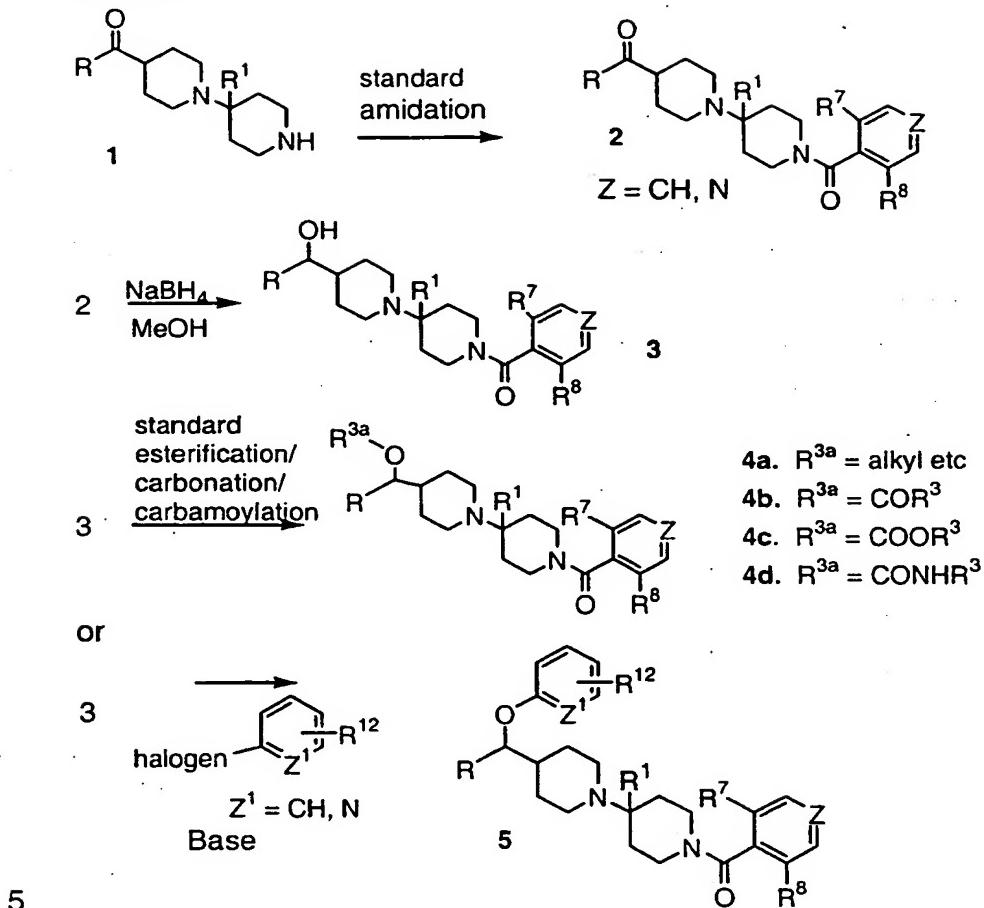
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding
15 compounds for purposes of the invention.

Compounds of the invention can be made by the procedures known in the art, for example by the procedures described in the following reaction schemes, by the methods described in the examples below, and by using the methods described in US patents 5,883,096; 6,037,352; 5,889,006;
20 5,952,349; and 5,977,138.

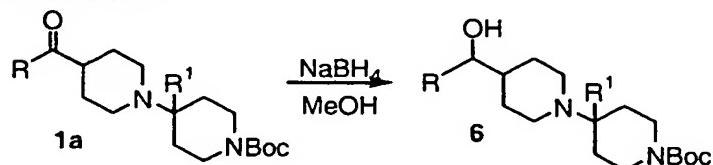
The following solvents and reagents may be referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic
25 anhydride (TFAA); 1-hydroxy-benzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et₃N); diethyl ether (Et₂O); tert-butoxy-carbonyl (BOC); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); dimethyl-sulfoxide (DMSO); p-toluene sulfonic acid (p-TSA); potassium bis(trimethylsilyl)-amide (KHMDA); 4-dimethylaminopyridine (DMAP);
30 N,N,N-diisopropylethylamine (Dipea); and 1-(3-dimethyl-aminopropyl)-3-ethyl carbodiimide hydrochloride (DEC). RT is room temperature.

Compounds of formula I and II wherein X is CHO(C=O)-(C₁-C₆)-alkyl, CHO(C=O)-(C₁-C₆)alkoxy, CHO(C=O)-NH-(C₁-C₆)alkyl, CHNR⁵(C=O)-(C₁-C₆)alkyl, CHNR⁵(C=O)-(C₁-C₆)alkoxy, CHNR⁵(C=O)-NH-(C₁-C₆)alkyl or -CHOR³ (and wherein R¹⁴, R¹⁵ and R¹⁶ are hydrogen)
35 are prepared according to Schemes 1-4:

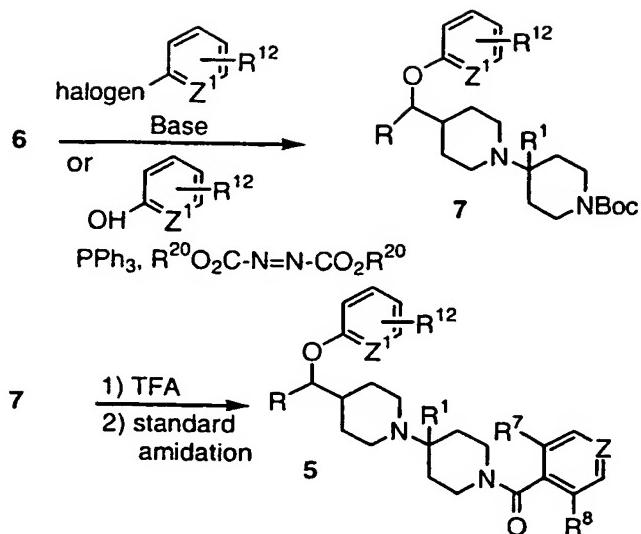
- 17 -

Scheme 1

Compounds of formula 3, wherein R, R⁷ and R⁸ are as defined for formula I, Z is CH or N, and R¹ is an alkyl group such as methyl were prepared as depicted in Scheme 1. Ketone 1, the synthesis of which was described in WO98/05292, was subjected to standard amidation with ArCOOH, EDCI or DEC, and HOBT, or ArCOCl, wherein Ar is R⁷, R⁸-substituted phenyl or pyridyl, followed by reduction with NaBH₄ to obtain 3. Derivatization of the free hydroxyl moiety with alkyl halides, acyl chlorides (R³COCl), alkyl chloroformates (CICOOR³) and isocyanides (O=C=NR³) afforded ethers 4a, esters 4b, carbonates 4c, and carbamates 4d, respectively, wherein R³ is a lower alkyl group. The aryloxy compounds, 5, were obtained after condensation of the hydroxyl 3 with phenyl or pyridyl halides in the presence of a base.

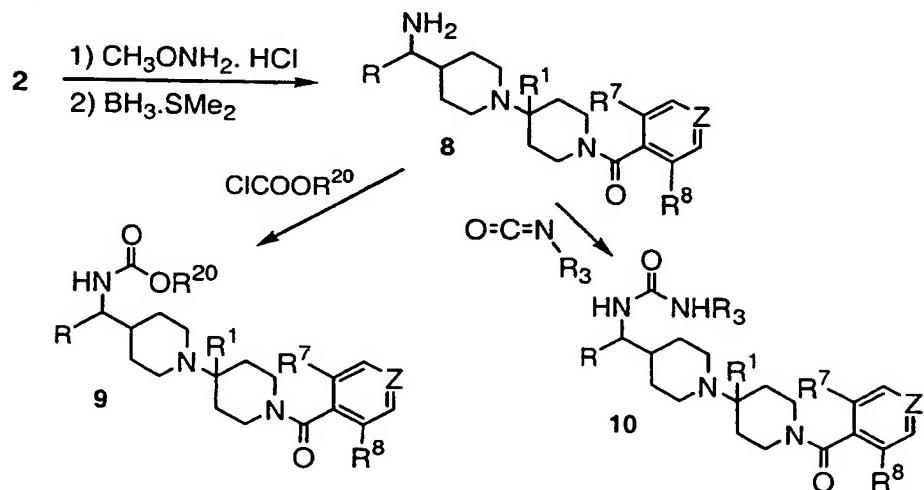
Scheme 2

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Alternatively, compounds of formula 5 can be prepared by reduction of the N-Boc ketone 1a to the alcohol 6 first, followed by functionalization of the free hydroxyl group with a halogen-substituted aryl in the presence of a base as shown in Scheme 2, or by a hydroxy-substituted aryl or heteroaryl (wherein Z¹ is as defined in Scheme 1) in the presence of PPh₃ and an azodicarboxylate of the formula R¹⁹O₂C-N=N-CO₂R²⁰, wherein R²⁰ is C₁-C₆ lower alkyl. Removal of the Boc protecting group and conversion to the amide is performed as in Scheme 1. This route allows the introduction of various aryloxy and heteroaryloxy moieties at R³ through the use of nucleophilic displacement or Mitsunobu-type reaction on intermediate 6.

Scheme 3

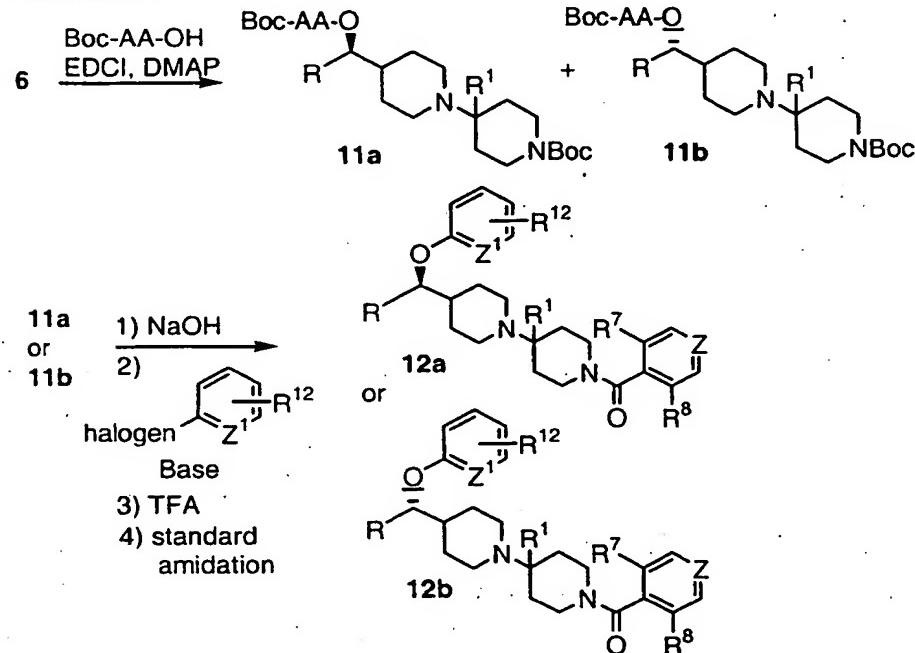


Compounds of formula 8, wherein R, R¹, R⁷, R⁸ and Z are as described in Scheme 1, were prepared by conversion of the ketone 2 to an oxime group with CH₃ONH₂·HCl, and reduction with BH₃·S(CH₃)₂ to

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provide amine **8**. Derivatization of the free amine moiety with an alkyl chloroformate (ClCOOR^{20} , wherein R^{20} is C₁-C₆ alkyl) or an isocyanide ($\text{O}=\text{C}=\text{NR}^3$) affords carbamate compounds **9** and urea compounds **10**, respectively.

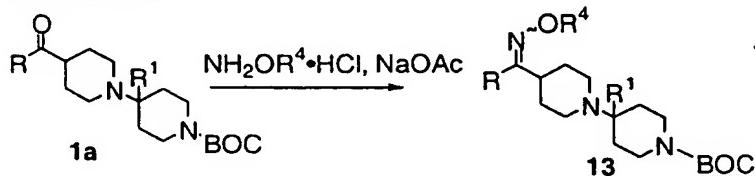
5 **Scheme 4**



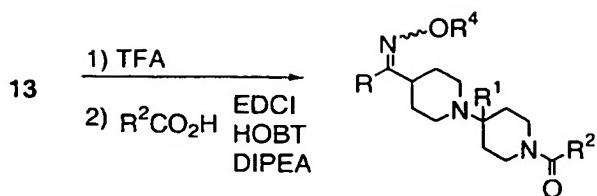
Preparation of chiral analogs was performed through chemical resolution. The alcohol **6** was coupled with a chiral Boc-protected amino acid to obtain diastereoisomers **11a** and **11b** which were separated by chromatography. The chiral auxiliary was then removed with NaOH for each diastereoisomer and the same sequence of reactions described in Scheme 2 was carried out on each individual enantiomer to obtain compounds **12a** and **12b**.

Oximes of formula I or II wherein X is $\text{C}=\text{NOR}^4$ are prepared from the corresponding ketones from any of several methods known to those skilled in the art.

Scheme 5:



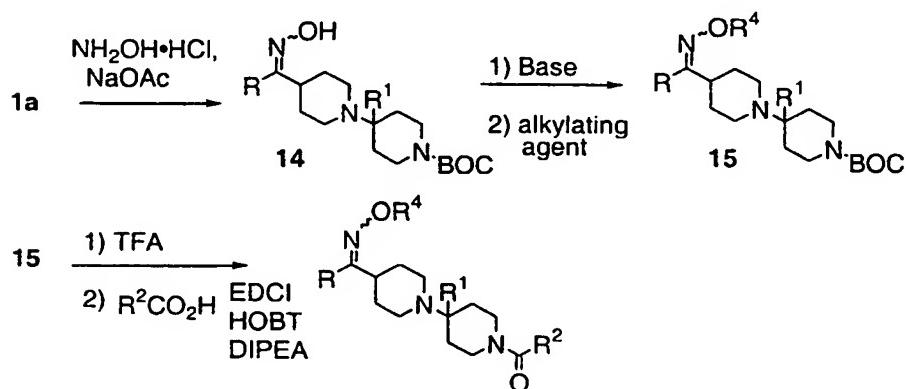
- 20 -



In Scheme 5, the ketone **1a**, wherein R and R¹ are as defined for formula I and II, is dissolved in a solvent such as CH₃OH or ethanol and treated with an R⁴-substituted hydroxylamine such as O-methylhydroxylamine hydrochloride in the presence of a base such as sodium acetate. The resulting mixture of Z- and E-O-substituted oximes **13** can be separated or the mixture carried through and separated at the end. The BOC protecting group is removed by treatment with an acid such as aqueous HCl or trifluoroacetic acid, and the resulting amine is coupled to an acid under standard conditions to obtain a compound of formula I or II.

5 The resulting mixture of Z- and E-O-substituted oximes **13** can be separated or the mixture carried through and separated at the end. The BOC protecting group is removed by treatment with an acid such as aqueous HCl or trifluoroacetic acid, and the resulting amine is coupled to an acid under standard conditions to obtain a compound of formula I or II.

10 **Scheme 6:**



Alternatively, the ketone **1a** can be treated with HONH₂·HCl under similar conditions to yield, after separation, the E- and Z-oximes. Each

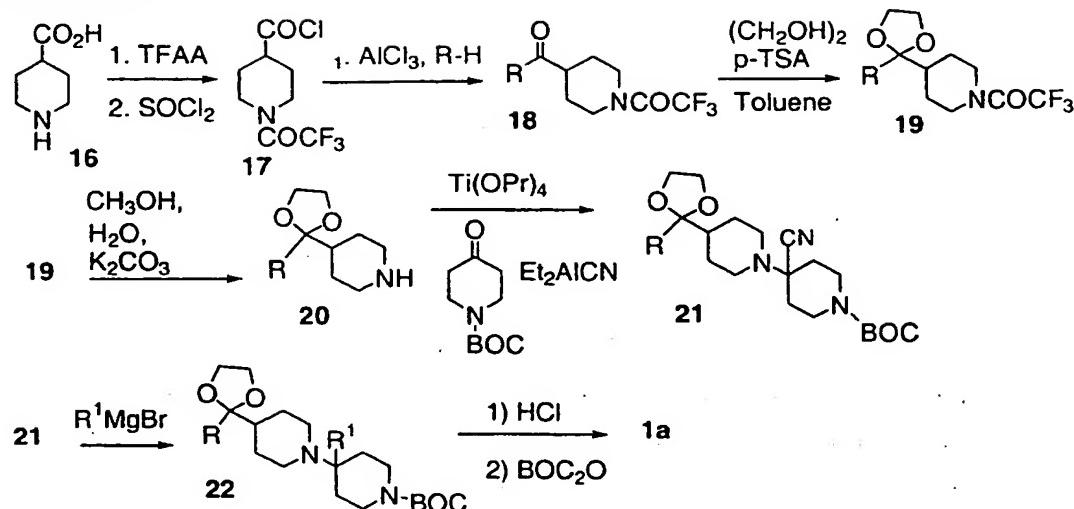
15 The ketone starting material of formula **1a** can be prepared by known methods as shown in Schemes 7 and 8.

15 The ketone starting material of formula **1a** can be prepared by known methods as shown in Schemes 7 and 8.

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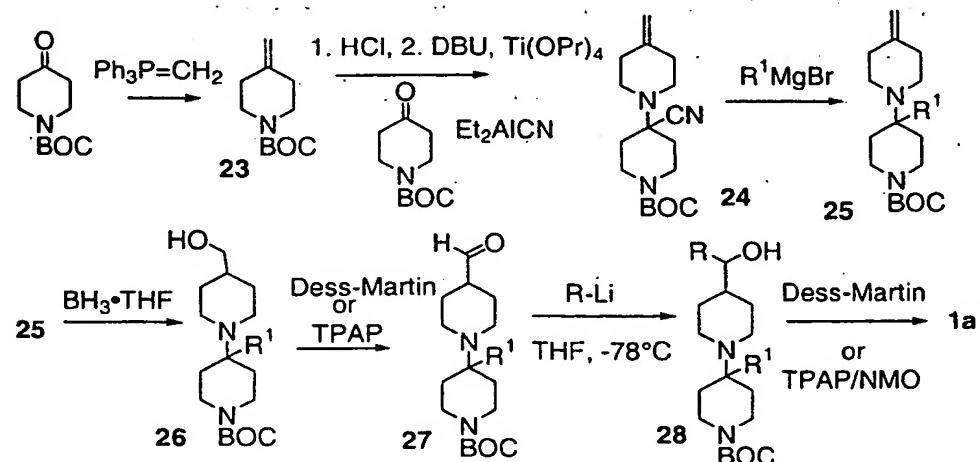
- 21 -

Scheme 7:



In Scheme 7, Friedel-Crafts condensation of N-trifluoroacetyl-
 5 isonipecotoyl chloride **17** and an aromatic group R-H in the presence of a suitable catalyst such as AlCl_3 and optionally in a solvent such as CH_2Cl_2 yields a ketone **18** which is converted to its ethylene ketal **19** under standard conditions. The N-trifluoroacetyl group is removed and the resulting free amine **20** is treated with N-BOC-piperidine-4-one in the
 10 presence of a dehydrating agent such as titanium isopropoxide followed by treatment with diethylaluminum cyanide to give an aminonitrile **21**. The aminonitrile is treated with a grignard reagent ($\text{R}^1\text{Mg-halide}$) such as CH_3MgBr or vinylmagnesium bromide to give the alkylated product **22**. The ketal is removed by treatment with aqueous acid followed by re-protection
 15 under standard conditions using BOC anhydride to give **1a**.

Scheme 8:

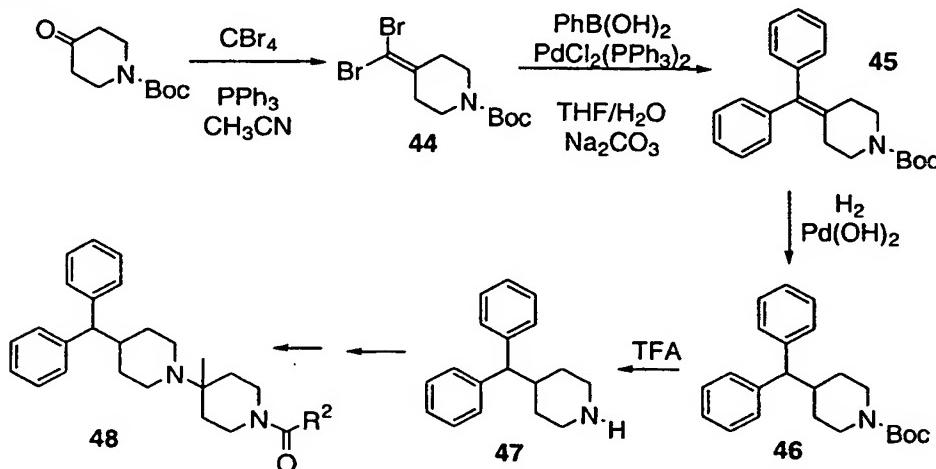


Alternatively, **23**, prepared via Wittig olefination of N-BOC-piperidone (Chen et al, Tetrahedron Lett., 37, 30 (1996), 5233-5234), is transformed to

intermediate 25 by analogy to the procedure described in Scheme 7. 25 is converted to alcohol 26 by hydroboration/oxidation. Alcohol 26 is treated with a suitable oxidant such as a mixture tetrapropylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO) to give 5 aldehyde 27. The aldehyde is treated with an aryllithium reagent in a suitable solvent such as ether or THF and the resulting alcohol 28 is treated with an oxidizing agent such as Dess-Martin periodinane or TPAP/NMO to give the desired ketone.

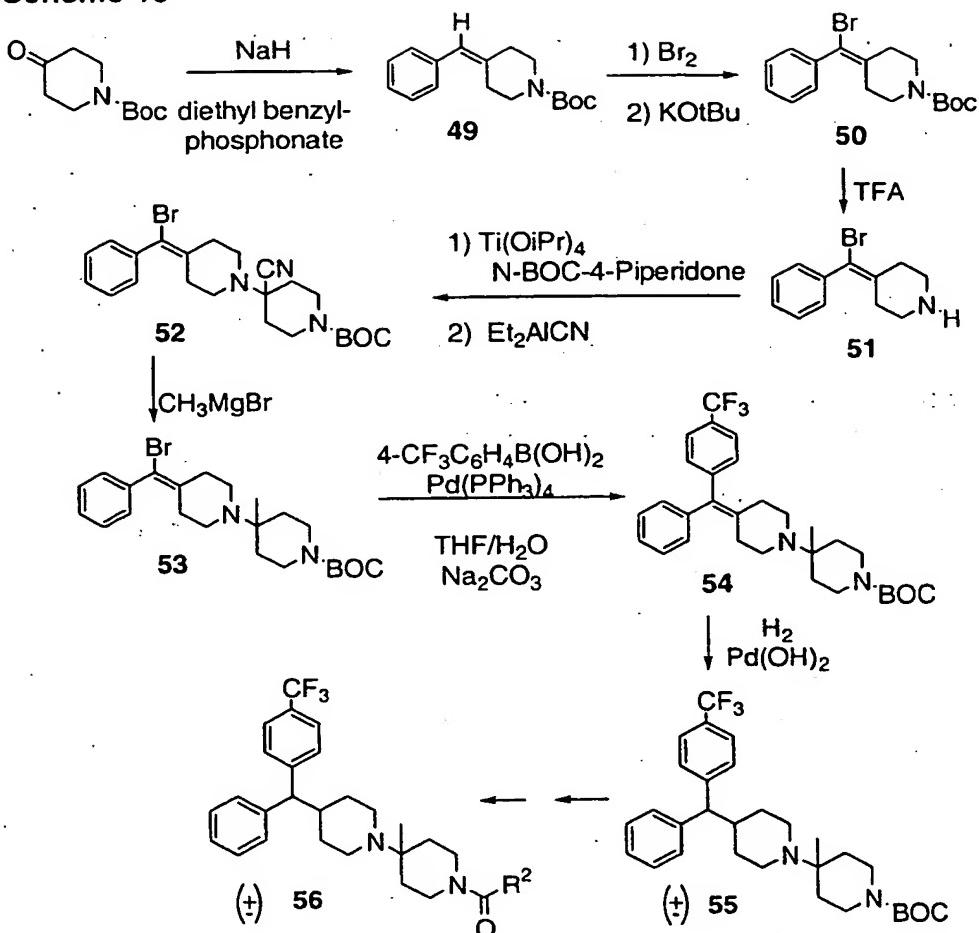
Compounds of formula I or II wherein X is $-C(R^{13})(R^{19})-$, wherein R 10 and R¹⁹ are the same, or wherein R and R¹⁹ are different are prepared according to schemes 9 and 10, respectively. The schemes are exemplified by processes wherein R and R¹⁹ are each phenyl and wherein R is phenyl and R¹⁹ is CF₃-phenyl, respectively, but the general procedures apply to other R and R¹⁹ groups.

15 **Scheme 9**



N-BOC-4-piperidone is treated with CBr₄ to obtain the di-bromo compound of formula 44, which is then treated with phenylboronic acid to obtain the BOC-protected diphenylmethylenepiperidine of formula 45. The 20 methylene bond is reduced using standard conditions to obtain the BOC-protected diphenylmethyl-piperidine of formula 46, the BOC group is removed and the amine of formula 47 is treated as described for compounds 20-22 of Scheme 7, the BOC group is removed by treatment with TFA, and the resultant amine subjected to a standard amidation 25 procedure, e.g., treatment with a reagent R²COOH and coupling agents such as EDCI, HOBT and a base, to obtain the compounds of formula 48.

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Scheme 10

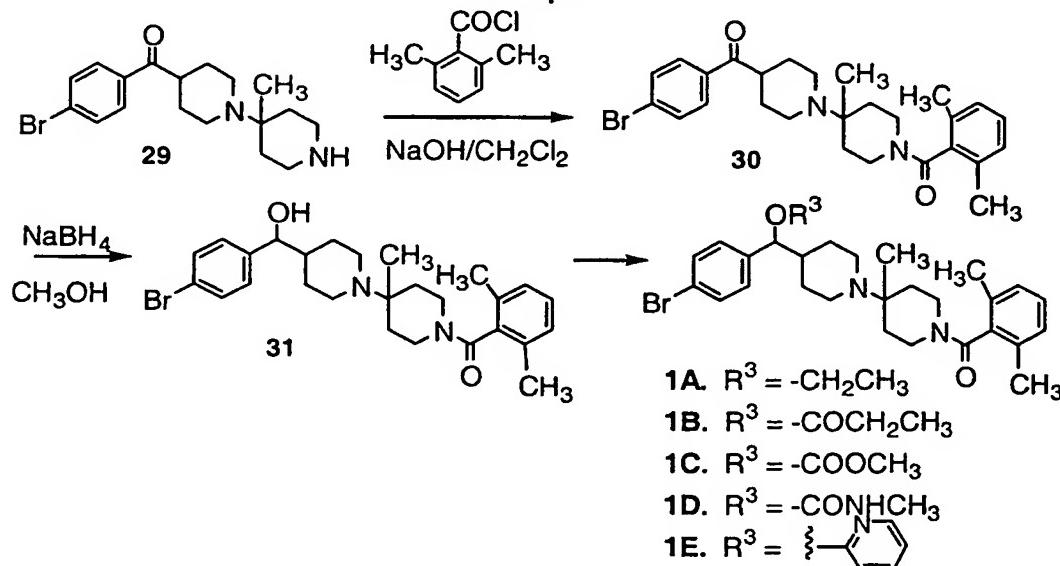
N-BOC-4-piperidone is treated with a reagent such as diethyl

- 5 benzylphosphonate to obtain the phenylmethylenepiperidine of formula 49, which is then brominated to obtain the bromophenylmethylenepiperidine of formula 50. The BOC protecting group is removed using standard conditions, e.g., treatment with TFA, to obtain amine 51, and the amine 51 is treated as described for compounds 20-22 of Scheme 7 to obtain the
- 10 aminonitrile 52, then the protected amine 53. The amine 53 is treated with a reagent such as 4-CF₃-phenylboronic acid to obtain compound 54 and the methylene bond is reduced using standard conditions to obtain racemic 55. The BOC group is removed by treatment with TFA, and the resultant amine subjected to a standard amidation procedure, e.g., treatment with a
- 15 reagent R²COOH and coupling agents such as EDCI, HOBT and a base, to obtain the racemic compounds of formula 56.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of

the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

Example 1



5 A solution of free amine **29** (1.45 g, 3.97 mmol) and 2,6-dimethylbenzoyl chloride (840 mg, 5.0 mmol) in aqueous 1 N NaOH (20 ml) and CH₂Cl₂ (20 ml) was stirred overnight at RT. The reaction mixture was extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated under high vacuum to provide **30** (1.97 g, 97%), as a slightly yellow foam.

10 To a solution of ketone **30** (550 mg, 1.11 mmol) in CH₃OH (6 ml) was added NaBH₄ (60 mg, 1.59 mmol) and the solution was stirred overnight at RT. The reaction mixture was then poured into 0.1 N NaOH, extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated to give **31** (543 mg, 98%), as a slightly yellow foam.

15 **Example 1A:**

To a solution of alcohol **31** (50 mg, 0.10 mmol) in anhydrous DMF (0.5 ml) was added NaH (6.0 mg, 0.25 mmol) followed by ethyl iodide (12 μ l, 0.15 mmol) and the reaction was stirred 4 h at 40 °C. The reaction mixture was poured into aqueous 0.1 N NaOH, extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated. Purification by preparative chromatography (eluting with CH₂Cl₂/CH₃OH, 9:1) yielded **1A** (31 mg, 59%) as a colorless oil: ¹H-NMR (300 MHz, CDCl₃) δ 7.39 (br d, *J* = 8.4 Hz, 2H), 7.02-7.12 (m, 3H), 6.95 (m, 2H), 3.94 (m, 1H), 3.79 (d, *J* = 7.2 Hz, 1H), 3.10-3.35 (m, 4H), 2.60-3.00 (m, 3H), 2.19 (br s, 6H), 1.60-2.10 (m, 5H), 1.05-1.50 (m, 5H), 1.08 (br t, 3H), 0.94 (s, 3H); HRMS (MH⁺) 527.2271.

Example 1B:

To a solution of alcohol **31** (50 mg, 0.10 mmol) and pyridine (16.2 μ L, 0.20 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added propionyl chloride (30 μ L, 0.30 mmol) and the solution was stirred overnight at RT. The
5 reaction mixture was treated as for **1A** to give, after preparative chromatography (eluting with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 9:1), **1B** (44.7 mg, 81%) as a colorless oil: ^1H -NMR (300 MHz, CDCl_3) δ 7.42 (br d, J = 8.2 Hz, 2H),
7.05-7.15 (m, 3H), 6.97 (m, 2H), 5.40 (d, J = 7.8 Hz, 1H), 4.09 (m, 1H),
3.43 (m, 1H), 3.23 (m, 1H), 2.96 (m, 1H), 2.82 (m, 1H), 2.70 (m, 1H), 2.21
10 (d, 3H), 1.60-2.10 (m, 5H), 1.05-1.45 (m, 5H), 1.08 (m, 3H), 0.95 (s, 3H);
HRMS (MH^+) 555.2230.

Example 1C: To a solution of alcohol **31** (29.4 mg, 0.059 mmol) and pyridine (9.5 μ L, 0.118 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was added methylchloro-formate (13.8 μ L, 0.18 mmol) and the solution was stirred
15 overnight at RT. The reaction mixture was treated as for **1A** to give, after preparative chromatography (eluting with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 9:1), **1C** (15 mg, 46%) as a colorless oil: ^1H -NMR (300 MHz, CDCl_3) δ 7.46 (br d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.09 (m, 1H), 6.98 (m, 2H), 5.21 (d, J = 7.2 Hz, 1H), 4.09 (m, 1H), 3.71 (m, 3H), 3.45 (m, 1H), 3.24 (m, 1H), 2.97
20 (m, 1H), 2.82 (m, 1H), 2.70 (m, 1H), 2.22 (br s, 3H), 1.60-2.10 (m, 5H),
1.10-1.50 (m, 5H), 0.95 (s, 3H); HRMS (MH^+) 557.2017.

Example 1D:

A solution of alcohol **31** (30 mg, 0.060 mmol), pyridine (9.7 μ L, 0.12 mmol) and methylisocyanate (40 μ L, 0.68 mmol) in anhydrous THF (0.3 ml) was stirred 5 h at 45 °C. The reaction mixture was treated as for **1A** to give, after preparative chromatography (eluting with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 9:1), **1D** (25 mg, 75%) as a colorless oil: ^1H -NMR (300 MHz, CDCl_3) δ 7.42 (br d, J = 8.2 Hz, 2H), 7.05-7.15 (m, 3H), 6.98 (m, 2H), 5.34 (m, 1H), 4.08 (m, 1H), 3.44 (m, 1H), 3.24 (m, 1H), 3.19 (s, 3H), 2.96 (m, 1H), 2.65-2.85 (m, 2H), 2.20 (br s, 3H), 1.55-2.10 (m, 5H), 1.10-1.50 (m, 5H), 0.95 (s, 3H);
30 HRMS (MH^+) 556.2169.

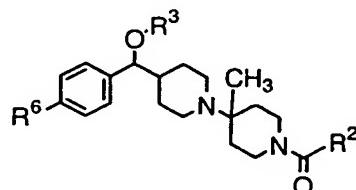
Example 1E:

A solution of alcohol **31** (50 mg, 0.10 mmol), NaH 60% in mineral oil (6 mg, 0.15 mmol), and 2-chloropyridine (28.2 μ L, 0.30 mmol) in anhydrous DMF (0.5 ml) was stirred 16 h at 90 °C. The reaction mixture was treated as for **1A** to give, after preparative chromatography (eluting with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 9:1), **1E** (50 mg, 86%) as a colorless oil: ^1H -NMR (300

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MHz, CDCl₃) δ 7.98 (m, 1H), 7.47 (br t, J = 7.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 6.95-7.15 (m, 3H), 6.65-6.80 (m, 2H), 5.74 (br d, J = 7.0 Hz, 1H), 4.09 (m, 1H), 3.44 (m, 1H), 3.24 (m, 1H), 2.65-3.05 (m, 3H), 2.22 and 2.23 (s, 3H), 1.60-2.15 (m, 5H), 1.10-1.50 (m, 5H), 0.87 (s, 5 3H); HRMS (MH⁺) 576.2230.

Using similar procedures, compounds of the following structure were prepared



10 wherein R³, R⁶ and R² are as defined in the table:

Ex.	R ⁶	R ³	R ²	HRMS (MH ⁺) found
1F	Br	-C(O)OCH ₂ CH ₃		571.2181
1G	Br	-C(O)CH ₃		541.2054
1H	Br	-C(O)-(CH ₂) ₂ CH ₃		569.2392
1I	Br	-C(O)NHCH ₂ CH ₃		572.2322
1J	Br			584.1786
1K	Br			577.2162
1L	Br			577.2183

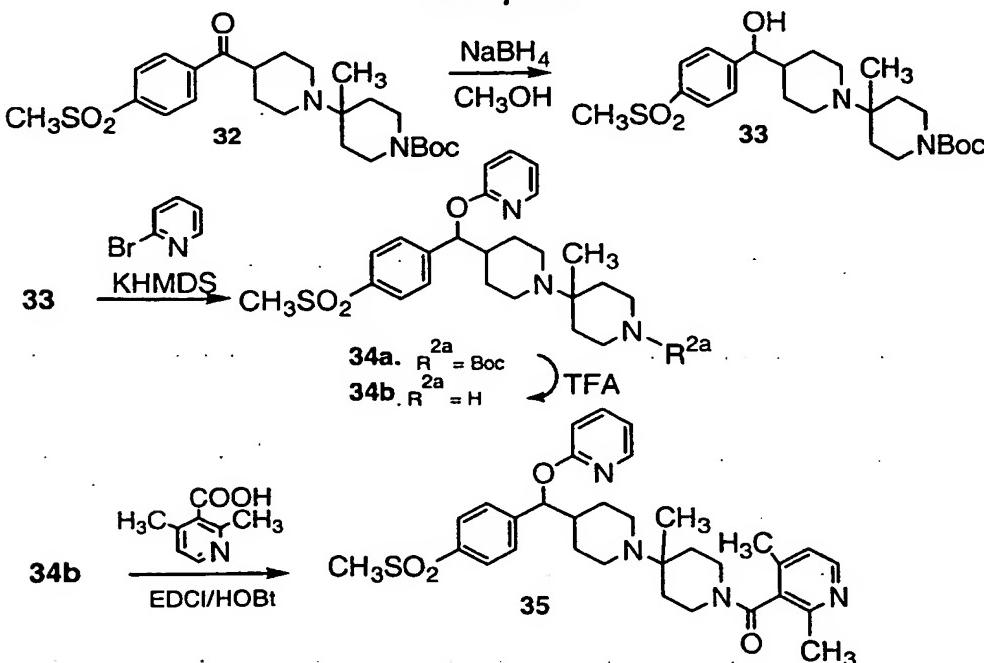
Additional data for compounds of Example 1:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
1J	7.49 (d, J = 8.4 Hz, 2H), 7.20-7.35 (m, 3H), 7.15 (m, 1H), 7.04 (m, 2H), 6.64 (d, J = 4.5 Hz, 1H), 5.58 and 5.60 (d, J = 7.2 Hz, 1H), 4.13 (m, 1H), 3.25-3.60 (m, 2H), 2.70-3.10 (m, 3H), 2.28 and 2.29 (s, 3H), 1.65-2.20 (m, 5H), 1.20-1.55 (m, 5H), 0.92 (br s, 3H)

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1K	8.39 (d, $J = 5.6$ Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.05-7.20 (m, 2H), 6.99 (m, 2H), 6.84 (m, 1H), 5.70 (d, $J = 7.8$ Hz, 1H), 4.11 (m, 1H), 3.43 (m, 1H), 3.25 (m, 1H), 2.65-3.05 (m, 3H), 2.23 and 2.25 (s, 3H), 1.55-2.10 (m, 5H), 1.10-1.50 (m, 5H), 0.88 (br s, 3H)
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Example 2



A solution of ketone **32** (0.60 g, 1.29 mmol) and NaBH₄ (60 mg, 1.59 mmol) in CH₃OH (5 ml) was stirred overnight at RT. The reaction mixture was poured into 0.1 N NaOH, extracted with CH₂Cl₂, dried over Na₂SO₄, and concentrated to give **33** (0.60 g, 100%), as a white foam.

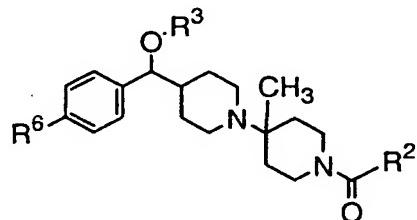
To a solution of alcohol **33** (543 mg, 1.2 mmol) in anhydrous toluene (4 ml) was added KHMDS, 0.5 N in toluene (2.6 ml, 1.30 mmol) followed, 10 min. later, by 2-bromopyridine (125 μ l, 1.30 mmol). The reaction was heated 5 h at 60 °C, cooled to RT and poured into 5% aqueous NaHCO₃ (25 ml). Extraction with CH₂Cl₂, drying over Na₂SO₄ and concentration afforded an oil which was purified by flash chromatography over silica gel (eluting with CH₂Cl₂/AcOEt/Et₃N 50:50:1 to 40:60:1) to yield **34a** (310 mg, 49%), as a yellow foam.

A solution of **34a** (310 mg, 0.57 mmol) in anhydrous CH₂Cl₂ (2 ml) and TFA (2 ml) was stirred 30 min. at RT. After concentration, the residue was taken up in aqueous 1 N NaOH, extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated to give **34b** (220 mg, 87%), as a white foam.

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A solution of free amine **34b** (85 mg, 0.19 mmol), 2,4-dimethyl-nicotinic acid (50 mg, 1.45 mmol), DEC (60 mg, 0.31 mmol), HOBT (50 mg, 0.37 mmol) and *N*-methylmorpholine (80 ml, 0.72 mmol) in anhydrous DMF (1 ml) was stirred overnight at 40 °C. After concentration, the residue was taken up in aqueous 0.1 N NaOH, extracted with CH₂Cl₂, and dried over Na₂SO₄. The residue obtained after concentration of the solvent was purified by preparative chromatography over silica gel (eluting with CH₂Cl₂/CH₃OH/NH₄OH, 96:4:1) to afford **35** (95 mg, 85%), as a colorless oil: ¹H-NMR (300 MHz, CDCl₃) δ 8.33 (d, *J* = 5.1 Hz, 1H), 7.99 (dd, *J* = 4.8 and 1.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.53 (m, 1H), 6.96 (d, *J* = 5.1 Hz, 1H), 6.75-6.85 (m, 2H), 4.15 (m, 1H), 3.45 (m, 1H), 3.30 (m, 1H), 3.02 (s, 3H), 2.99 (m, 2H), 2.79 (m, 1H), 2.47 and 2.48 (s, 3H), 2.45 (m, 1H), 2.25 and 2.26 (s, 3H), 1.65-2.15 (m, 5H), 1.15-1.55 (m, 5H), 0.90 (s, 3H); HRMS (MH⁺) 577.2858.

Using similar procedures, compounds of the following structure were prepared



wherein R³, R⁶ and R² are as defined in the table:

Ex.	R ⁶	R ³	R ²	HRMS (MH ⁺) found
2A	Br			599.1062
2B	Br			578.2006
2C	Br			577.2172
2D	Br			577.2172
2E	H ₃ CSO ₂ -			597.2296

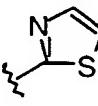
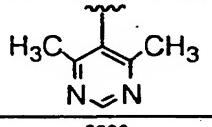
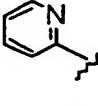
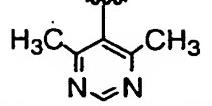
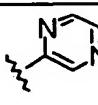
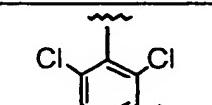
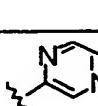
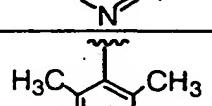
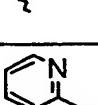
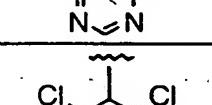
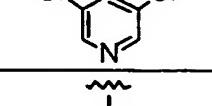
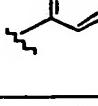
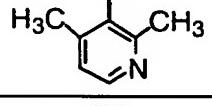
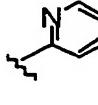
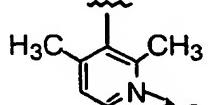
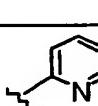
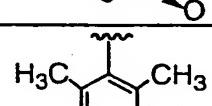
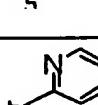
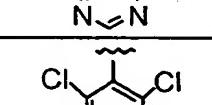
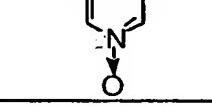
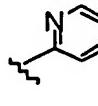
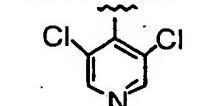
- 29 -

2F	H ₃ CSO ₂ -			578.2697
2G	F ₃ C-			567.2947
2H	H ₃ CSO ₂ -			576.2890
2I	H ₃ CSO ₂ -			593.2805
2J	F ₃ CO-			582.2969
2K	F ₃ CO-			584.2744
2L	F ₃ CO-			583.2913
2M	Br			580.2123
2N	Br			579.1986
2O	F ₃ CO-			599.2847
2P	Br			595.2114
2Q	Br			594.2072
2R	H ₃ CSO ₂ -			578.2792

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2S	H ₃ CSO ₂ ⁻			578.2801
2T	H ₃ CSO ₂ ⁻			594.2750
2U	H ₃ CSO ₂ ⁻			583.2426
2V	H ₃ CSO ₂ ⁻			576.2896
2W	H ₃ CSO ₂ ⁻			599.2362
2X	F ₃ C-			583.2905
2Y	F ₃ CO-			584.2848
2Z	F ₃ CO-			623.1790
2AA	Cl			533.2673
2BB	Cl			549.2646
2CC	Cl			573.1606
2DD	Cl			534.2637
2EE	Br			619.1062

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2FF	H ₃ CSO ₂ -			584.2375
2GG	F ₃ C-			568.2913
2HH	H ₃ CSO ₂ -			618.1722
2II	H ₃ CSO ₂ -			579.2749
2JJ	F ₃ C-			607.1871
2KK	F			517.2696
2LL	F			533.2916
2MM	F			518.2944
2NN	Cl			589.1534
2OO	F			573.1818
2PP	Br			591.2330
2QQ	Br			607.2291

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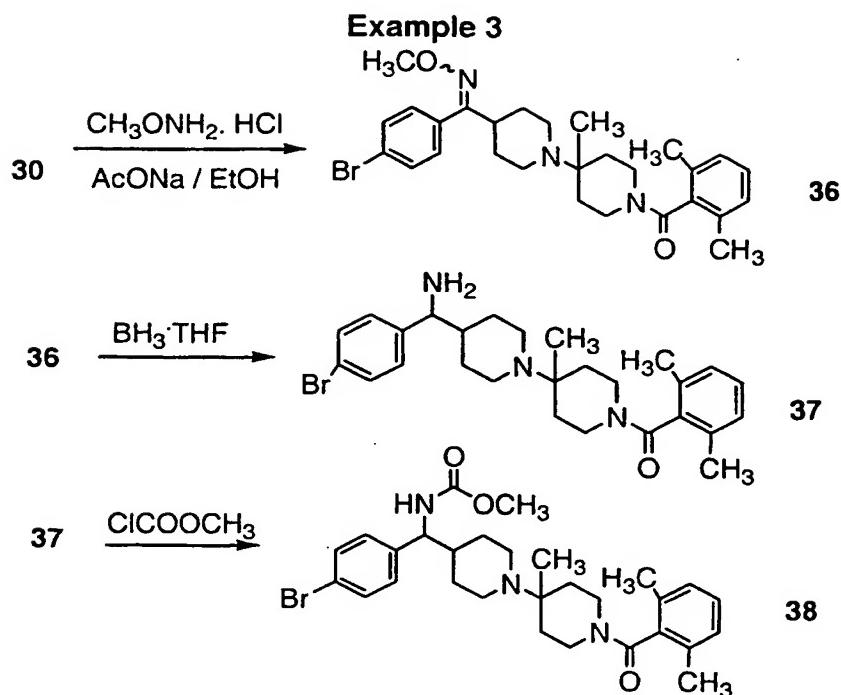
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2UU	F ₃ C-			583.2909
2VV	F ₃ C-			567.2961
2WW	F			532.3106
2XX	H			500.3023

Additional data for compounds of Example 2:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
2A	7.98 (m, 1H), 7.49 (br t, J = 7.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.01 (t, J = 8.4 Hz, 1H), 6.65-6.80 (m, 3H), 6.56 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 7.2 Hz, 1H), 3.95-4.20 (m, 1H), 3.89 and 3.92 (s, 2H), 3.30-3.55 (m, 2H), 3.12 (m, 1H), 2.70-3.00 (m, 2H), 1.65-2.10 (m, 5H), 1.20-1.60 (m, 5H), 0.95 and 0.99 (s, 3H)
2G	8.31 (d, 1H), 8.01 (d, 1H), 7.50 (m, 4H), 6.95 (d, 1H), 6.80 (m, 2H), 5.90 (d, 1H), 4.15 (d, 1H), 3.25-3.55 (m, 2H), 2.80-3.15 (m, 3H), 2.50 (d, 3H), 2.30 (d, 3H), 1.80-2.15 (m, 7H), 1.20-1.60 (m, 5H), 0.92 (s, 3H)

2K	7.97 (m, 1H), 7.45 (m, 1H), 7.32 (t, $J = 8.4$ Hz, 2H), 7.06 (m, 2 H), 7.01 (m, 1H), 6.60-6.75 (m, 4H), 5.77 and 5.79 (d, $J = 5.6$ Hz, 1H), 3.55 (m, 1H), 3.32 (m, 1H), 2.70-2.95 (m, 2H), 2.18 (s, 3H), 1.65-2.10 (m, 5H), 1.15-1.55 (m, 5H), 0.78 and 0.91 (s, 3H)
2M	8.29 (d, $J = 5.2$ Hz, 1H), 8.18 (m, 1H), 7.98 (br s, 1H), 7.89 (br s, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H), 6.92 (d, $J = 5.2$ Hz, 1H), 5.67 (d, $J = 7.2$ Hz, 1H), 4.07 (m, 1H), 3.43 (m, 1H), 3.26 (m, 1H), 2.65-3.05 (m, 3H), 2.41 and 2.42 (s, 3H), 2.20 (br s, 3H), 1.60-2.20 (m, 5H), 1.05-1.50 (m, 5H), 0.85 (br s, 3H)
2P	8.14 (d, $J = 6.8$ Hz, 1H), 8.02 (m, 1H), 7.51 (m, 1H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 6.98 (d, $J = 6.4$ Hz, 1H), 6.78 (m, 1H), 6.73 (m, 1H), 5.78 (d, $J = 6.8$ Hz, 1H), 4.17 (m, 1H), 3.43 (m, 1H), 3.32 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.75 (m, 1H), 2.44 and 2.46 (s, 3H), 2.23 and 2.25 (s, 3H), 1.65-2.10 (m, 5H), 1.15-1.50 (m, 5H), 0.90 (s, 3H)
2HH	8.49 (s, 2H), 8.26 (br s, 1H), 8.04 (br s, 1H), 7.80-7.95 (m, 3H), 7.53 (d, $J = 8.4$ Hz, 2H), 5.81 (d, $J = 6.8$ Hz, 1H), 4.16 (m, 1H), 3.30-3.50 (m, 2H), 2.94 (m, 2H), 2.80 (m, 1H), 1.75-2.15 (m, 5H), 1.25-1.50 (m, 5H), 0.89 (s, 3H)
2MM	8.93 (s, 1H), 8.04 (br d, $J = 4.8$ Hz, 1H), 7.50 (m, 1H), 7.32 (m, 2H), 6.97 (m, 2H), 6.78 (m, 1H), 6.72 (m, 1H), 5.82 (m, 1H), 4.21 (m, 1H), 3.25-3.50 (m, 2H), 2.93 (m, 2H), 2.78(m, 1H), 2.44 and 2.46 (s, 3H), 1.90-2.15 (m, 3H), 1.70-1.90 (m, 2H), 1.15-1.50(m, 5H), 0.90(s, 3H)
2NN	8.17 (s, 1H), 8.01 (br d, $J = 4.0$ Hz, 1H), 7.50 (br t, $J = 8.0$ Hz, 1H), 7.20-7.35 (m, 4H), 6.78 (t, $J = 6.8$ Hz, 1H), 6.71 (m, 1H), 5.80 (d, $J = 6.8$ Hz, 1H), 4.18 (m, 1H), 3.44 (m, 1H), 3.39 (m, 1H), 3.00 (m, 2H), 2.80 (m, 1H), 1.70-2.15 (m, 5H), 1.10-1.50 (m, 5H), 0.90 (s, 3H)
2PP	8.37 (d, $J = 6.0$ Hz, 1H), 7.83 (br d, $J = 4.6$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 6.0$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 6.97 (d, $J = 4.6$ Hz, 1H), 6.68 (br t, $J = 6.0$ Hz 1H), 5.89 (br d, $J = 6.8$ Hz, 1H), 4.20 (m, 1H), 3.20-3.50 (m, 2H), 2.97 (m, 2H), 2.78 (m, 1H), 2.47 and 2.49 (s, 3H), 2.23 and 2.26 (s, 3H), 2.23 (s, 3H), 1.65-2.15 (m, 5H), 1.15-1.55 (m, 5H), 0.90 (s, 3H)

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To a solution of ketone **30** (1.5 g, 3.22 mmol) in CH_3OH (50 ml) was added sodium acetate (5.0 g, 47 mmol) and *O*-Methyl hydroxylamine hydrochloride (3.26 g, 47 mmol), and the solution was stirred at RT for 24 h. The resulting mixture was then poured into aqueous NaOH and extracted with CH_2Cl_2 . The combined extracts were dried, concentrated and chromatographed to yield 1.50 g (94%) of oxime **36**, as a mixture of E and Z isomers.

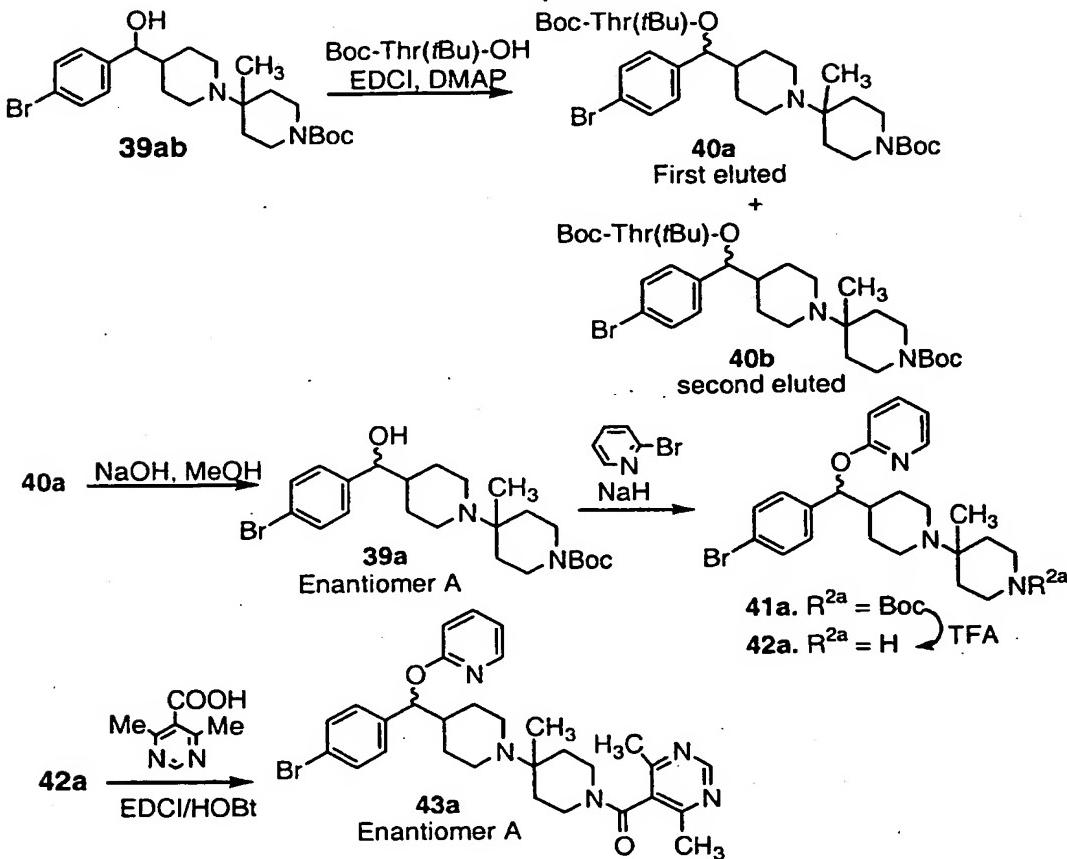
To a stirred solution of oxime **36** (0.200 g, 0.380 mmol) in THF (5 ml) was added $\text{BH}_3 \cdot \text{THF}$ (1.0 M solution in THF) at 0 °C and the solution was then warmed to RT and stirred for 1 h. The reaction mixture was then cooled to 0°C and a solution of 1N KOH in CH_3OH (5 ml) was added. The reaction was warmed slowly to 60°C for 2 h, cooled to RT, quenched with water and extracted with CH_2Cl_2 . Combined organic layers were concentrated and chromatographed over silica gel (eluting with 20% EtOH/EtOAc) to afford 0.100 g (50%) of amine **37**.

To a stirred solution of amine **37** (0.015 g, 0.030 mmol) was added pyridine (0.5 ml) and ClCOOCH_3 (0.25 ml), and the solution was stirred overnight. It was then poured into water, extracted with EtOAc, dried, concentrated and purified by preparative chromatography to give 0.010 g of desired product **38**: $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.45 (d, 2H), 7.05-7.12 (m, 3H), 6.95 (d, 2H), 4.95 (m, 1H), 4.45 (m, 1H), 4.15 (m, 1H), 3.62 (s,

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3H), 3.47 (m, 1H), 3.25 (m, 1H), 2.88-3.10 (m, 3H), 2.25 (s, 6H), 1.20-2.10 (m, 12H), 0.90 (s, 3H); HRMS (MH⁺) 558.3013.

Example 4

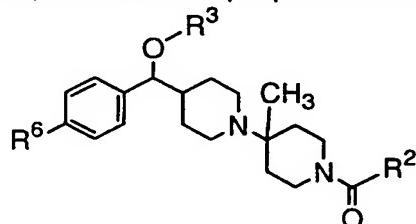


- 5 A solution of alcohol 39ab (660 mg, 1.41 mmol), Boc-Thr(t-Bu)-OH (413 mg, 1.50 mmol), DEC (290 mg, 1.50 mmol) and DMAP (190 mg, 1.55 mmol) in anhydrous CH₂Cl₂ (5 ml) was stirred overnight at RT. The reaction mixture was poured into aqueous saturated NaHCO₃, extracted with CH₂Cl₂, and dried over Na₂SO₄. The residue obtained after concentration of the solvent was subjected to flash chromatography over silica gel (eluting with CH₂Cl₂/acetone, 9:1) to afford, in order of elution: (i) first 40a (391 mg, 38%), as a white foam; (ii) second 40b (391 mg, 38%), as a white foam.
- 10 To a solution of diastereoisomer 40a (391 mg, 0.54 mmol) in CH₃OH (3 ml) was added NaOH (110 mg, 2.75 mmol; 5 equiv.) and the solution was stirred at 65 °C for 3 h. The final mixture was then poured into aqueous 0.1 N NaOH and extracted with CH₂Cl₂ to yield 39a (Enantiomer A) (246 mg, 98%) as a white foam. (Following the same procedure, 40b gave 39b (Enantiomer B). 40a gives 43a (Enantiomer A) and 40b gives 43b (Enantiomer B.).)

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- A solution of alcohol **39a** (210 mg, 0.45 mmol), NaH 60% in mineral oil (23 mg, 0.96 mmol), and 2-bromopyridine (60 μ l; 0.62 mmol) in anhydrous DMF (1.5 ml) was stirred 2 h at 75 °C. The reaction mixture was poured into aqueous sat'd NaHCO₃, extracted with CH₂Cl₂, dried over Na₂SO₄ and purified by flash chromatography over silica gel (eluting with CH₂Cl₂/AcOEt/Et₃N, 60:40:0.5 to 40:60:0.5) to afford **41a** (143 mg, 59%).
- Removal of the Boc-protecting group in **41a** (93 mg, 0.17 mmol) proceeded as for **34b** to provide **42a** (68 mg, 91%), as a white foam.
- The amine **42a** (50 mg, 0.11 mmol) was coupled with 4,6-dimethyl-pyrimidine-5-carboxylic acid following the conditions described for the synthesis of **35** to yield **43a** (28 mg, 44%). ¹H-NMR (300 MHz, CDCl₃) δ 8.92 (s, 1H), 8.02 (m, 1H), 7.51 (m, 1H), 7.51 (br t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.78 (m, 1H), 6.73 (m, 1H), 5.78 (m, 1H), 4.19 (m, 1H), 3.41 (m, 1H), 3.36 (m, 1H), 2.94 (m, 1H), 2.78 (m, 1H), 2.44 and 2.46 (s, 3H), 1.65-2.15 (m, 5H), 1.15-1.50 (m, 5H), 0.90 (s, 3H); HRMS (MH⁺) 578.2140.

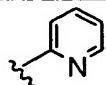
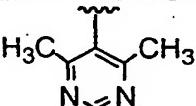
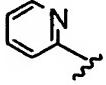
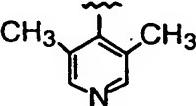
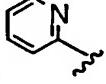
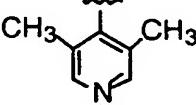
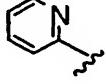
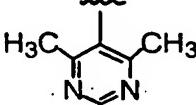
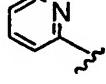
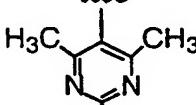
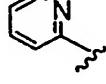
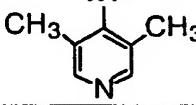
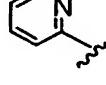
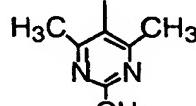
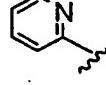
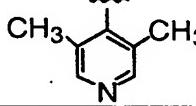
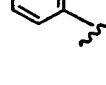
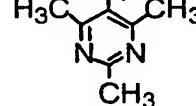
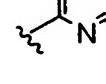
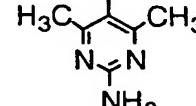
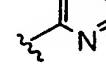
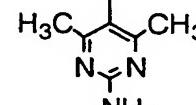
The following compounds were prepared via similar methods:



wherein R³, R⁶ and R² are as defined in the table:

Ex.	Enantiomer	R ⁶	R ³	R ²	HRMS (MH ⁺) found
4A	A	Br			577.2172
4B	B	Br			577.2162
4C	B	Br			578.2119
4D	A	F ₃ CO-			584.2864

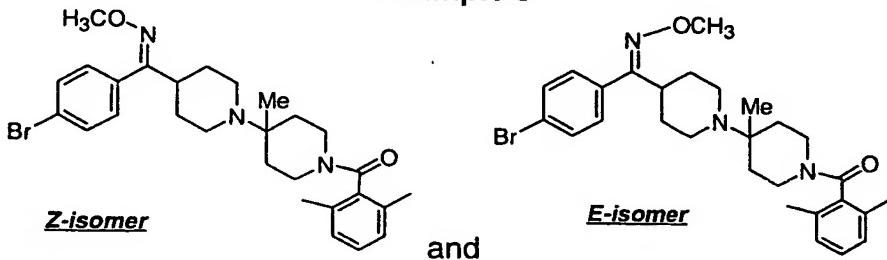
- 37 -

4E	B	F ₃ CO-			583.2862
4F	A	F ₃ CO-			583.2904
4G	A	F ₃ CO-			599.2857
4H	A	F ₃ CO-			598.2994
4I	B	F ₃ CO-			598.3000
4J	A	Cl			534.2639
4K	A	Cl			548.2784
4L	B	Cl			534.2644
4M	B	Cl			548.2784
4N	A	F ₃ CO-			599.2947
4O	B	F ₃ CO-			599.2947

Additional data for compounds of Example 4:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
4G	8.05 (m, 1H), 7.97 (s, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.81 (t, J = 6.4 Hz, 1H), 6.76 (m, 1H), 5.87 (m, 1H), 4.19 (m, 1H), 3.30-3.50 (m, 2H), 2.99 (m, 2H), 2.79 (m, 1H), 2.20 and 2.22 (s, 3H), 1.70-2.15 (m, 5H), 1.15-1.50 (m, 5H), 0.91 (s, 3H)
4I	8.03 (m, 1H), 7.53 (m, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.79 (t, J = 6.8 Hz, 1H), 6.73 (m, 1H), 5.87 (m, 1H), 4.19 (m, 1H), 3.42 (m, 1H), 3.37 (m, 1H), 2.98 (m, 2H), 2.80 (m, 1H), 2.41 and 2.43 (s, 3H), 1.90-2.15 (m, 3H), 1.70-1.90 (m, 2H), 1.20-1.50 (m, 5H), 0.91 (s, 3H)

Example 5



- 5 1) Trifluoroacetic anhydride (TFAA) (300 ml) is added to isonipecotic acid (96 g) at 0°C and the reaction mixture is heated at reflux for 4h. Excess TFAA is removed under vacuo, the reaction mixture is taken up in EtOAc, washed with water and concentrated to give 160 g of the amide. 50 g of this amide is treated with SOCl₂ (300 ml) and the reaction mixture
- 10 heated at reflux overnight. Excess thionyl chloride is then removed under vacuo to give 54 g of the acid chloride.
- 2) AlCl₃ (11g) is added slowly to a solution of the product of step 1 (10 g) in bromobenzene (40 ml) at ambient temperature and the reaction mixture is heated at reflux for 4 h. It is then cooled and poured into a
- 15 mixture of conc. HCl and ice, and the product is extracted with EtOAc. The organic layer is separated and washed with water, half saturated NaHCO₃ solution and concentrated to give 16.21 g of the desired ketone.
- 3) The product of step 2 (16.21 g) is dissolved in toluene (200 ml) containing ethylene glycol (25 ml) and p-toluenesulfonic acid (0.5 g). The
- 20 reaction mixture is heated at reflux with azeotropic removal of water until no further water is collected. The reaction mixture is concentrated to give 17.4 g of the desired ketal.

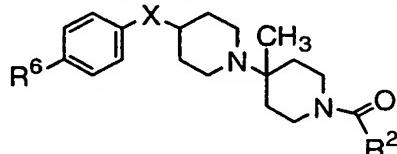
- 4) The crude product of step 3 (17.4 g) is dissolved in CH₃OH (100ml) and to this is added water (25 ml) and K₂CO₃ (12 g) and the reaction mixture is stirred at ambient temperature overnight. The reaction mixture is diluted with water and extracted with EtOAc. The organic layer is
- 5 separated, washed with water and brine, and concentrated to give 12.55 g of the desired amine.
- 5) To a stirred solution of the product of step 4 (7.2 g, 23 mmol) and N-BOC-piperidine-4-one (4.8 g, 24 mmol) in 1,2-dichloroethane (20 ml) is added titanium isopropoxide (6.7 ml, 32.3 mmol) and the mixture is stirred
- 10 for 12 h at RT. The reaction mixture is concentrated and a 1.0 M solution of diethyl aluminium cyanide (35 ml) is added at RT and stirred for 3 h. The reaction mixture is then diluted with EtOAc, quenched with water (5 ml) and stirred for 2 h. The mixture is then filtered through celite and the resulting filtrate is concentrated and chromatographed with 30 % EtOAc/hexanes to
- 15 afford 7.3 g (63%) of the desired cyanide.
- 6) To a stirred solution of the product of step 5 (7.3 g, 14.03 mmol) in THF (100 ml) is added a 3.0M solution CH₃MgBr in Et₂O (14.0 ml, 42 mmol) at RT and the mixture is stirred for 2 h. The reaction mixture is then quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The extracts are concentrated to afford 7.0 g of desired methylated compound.
- 20 7) The crude ketal of step 6 is dissolved in EtOAc (100 ml) and 6 N HCl (40 ml) and conc. HCl (10 ml) is added and the mixture stirred at RT for 24 h. The reaction mixture is then neutralised with 20%NaOH and extracted with EtOAc, dried and concentrated to yield 5.0 g (98%) of amine.
- 25 8) To a stirred solution of the product of step 7 (5.0 g, 13.6 mmol) in Et₂O (200 ml) is added 10% NaOH (50 ml) and BOC₂O, and the mixture is stirred at RT overnight. The layers are separated and the organic layer is washed with brine, dried, concentrated and chromatographed with 20% EtOAc/hexanes to yield 5.1 g (79%) of the desired product.
- 30 9). To a stirred solution of the product of step 8 (1.5 g, 3.22 mmol) in CH₃OH (50 ml) is added sodium acetate (5.0 g, 47 mmol) and O-Methyl hydroxylamine hydrochloride and the mixture is stirred at RT for 24 h. The resulting mixture is then poured into aqueous NaOH and extracted with CH₂Cl₂. The combined extracts are dried, concentrated and
- 35 chromatographed to yield 1.5 g (94%) of oxime as a mixture of E and Z isomers.
- 10) To a stirred solution of the product of step 9 (1.5 g, 3.0 mmol) in CH₂Cl₂ (10 ml) is added TFA (3 mL) and the mixture is stirred at RT for 2 h.

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The reaction mixture is concentrated and poured into 10% NaOH and extracted with CH₂Cl₂. The combined extracts are dried concentrated to afford 1.2 g (100%) of amine.

- 11) To stirred solution of the product of step 10 (1.3 g, 3.2 mmol) in
 5 CH₂Cl₂ is added 2,6-dimethylbenzoic acid (0.74 g, 4.96 mmol), EDCI (0.94 g, 4.94 mmol), DIPEA (0.84 g, 6.58 mmol) and HOBT (0.66g, 4.94 mmol) and the mixture is stirred for 12 h at RT. The reaction mixture is quenched with NaHCO₃ and extracted with CH₂Cl₂. The combined extracts are dried and concentrated to yield 1.6 g of oxime as a mixture of E and Z isomers.
 10 The isomers are separated by chromatography by eluting with CH₂Cl₂:Et₂O (4:1) to afford 0.77 g of E isomer and 0.49 g of Z isomer.
 E isomer: 300 MHz-¹H NMR (CDCl₃) δ 7.5 (d, 2H), 7.23 (m, 2H), 7.10 (m, 1H), 6.90 (d, 2H), 4.03 (m, 1H), 3.90 (s, 3H), 3.55 (m, 1H), 3.20 (m, 3H), 3.00 (m, 3H), 2.82 (m, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 2.15 (m, 3H), 1.80-1.20 (m, 5H), 0.92 (s, 3H); MS FAB+ observed= 526.2070; estimated = 526.2069
 15 Z isomer: 300 Mhz -¹H NMR (CDCl₃) δ 7.50 (d, 2H), 7.15 -6.95 (m, 5H), 4.15 (m, 1H), 3.80 (s, 3H), 3.45 (s, 3), 3.25 (s, 3H), 3.00 (m, 2H), 2.24 (s, 3H), 2.25 (s, 3H), 2.10 (m, 2H), 1.80- 1.50 (m, 7H), 0.92 (s, 3H);
 20 MS FAB+ observed= 526.2072; estimated = 526.2069.

The following compounds were prepared via similar methods:



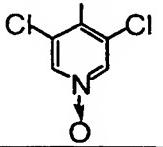
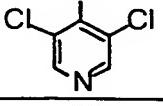
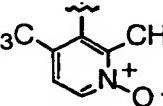
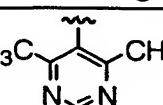
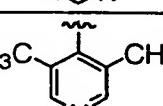
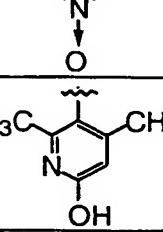
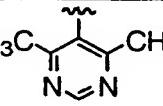
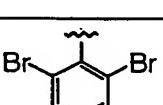
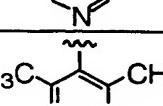
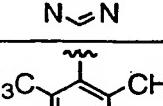
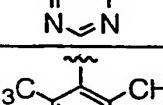
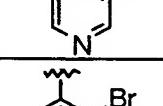
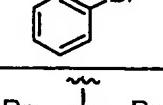
wherein X, R⁶ and R² are as defined in the table:

Ex.	R ⁶	X	R ²	HRMS (MH ⁺) found
5A (mixture E/Z)	Br			529.1017
5B (mixture E/Z)	Br			549.1023
5C	Br			542.2210
5D	Br			549.1011

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5E	Br			529.1128
5F	Br			530.1020
5G	Br			529.1017
5H	Br			542.1997
5I	Br			541.2178
5J	Br			527.2787
5K	Br			543.1000
5L	Br			528.1971
5M	Br			541.2194
5N	Br			542.2132
5O	Br			583.1061
5P	Br			595.1895
5Q	Br			596.1831
5R	Br			541.2188

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5S	Br	<chem>CH3CH2O[N+](=O)[C-]</chem>		597.4911
5T	Br	<chem>H3CO[N+](=O)[C-]</chem>		569.0909
5U	Br	<chem>CH3(CH2)2O[N+](=O)[C-]</chem>		571.2270
5V	Br	<chem>CH3(CH2)2O[N+](=O)[C-]</chem>		556.2291
5W	Br	<chem>CH3CH2O[N+](=O)[C-]</chem>		557.2119
5X	Br	<chem>CH3CH2O[N+](=O)[C-]</chem>		557.2124
5Y	Br	<chem>CC(C)CO[N+](=O)[C-]</chem>		570.2454
5Z	Br	<chem>CH3CH2O[N+](=O)[C-]</chem>		671.0058
5AA	Br	<chem>C1CCOC1[N+](=O)[C-]</chem>		568.2286
5BB	Br	<chem>CC(C)CO[N+](=O)[C-]</chem>		556.2286
5CC	Br	<chem>H3CO[N+](=O)[C-]</chem>		527.2015
5DD	Br	<chem>CH3CH2O[N+](=O)[C-]</chem>		592.1000
5EE	Br	<chem>H3CO[N+](=O)[C-]</chem>		656.9889

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5FF	Br	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>c1cc(Br)cnc1C(=O)OCC</chem>	686.9989
5GG	Br	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1nc(C)cnc1C(=O)OCC</chem>	556.2290
5HH	F ₃ C-	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1nc(C)cnc1C(=O)OCC</chem>	546.3056
5II	F ₃ C-	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1cc(C)cnc1C(=O)OCC</chem>	531.2956
5JJ	F ₃ C-	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>c1cc(C)cnc1C(=O)OCC</chem>	547.2902
5KK	F ₃ C-	<chem>CH3COc1nc(C)c(O)cc1</chem>	<chem>Cc1cc(C)cnc1C(=O)OC</chem>	517.2812
5LL	Br	<chem>CC(C)(C)C1=CC=CNC1C(=O)OCC</chem>	<chem>Cc1cc(C)cnc1C(=O)OCC</chem>	555.2336
5MM	Br	<chem>CC1=CC=CC1C(=O)OCC</chem>	<chem>Cc1cc(C)cnc1C(=O)OCC</chem>	567.2327
5NN	Br	<chem>CH3(CH2)2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1cc(C)cnc1C(=O)OCC</chem>	555.2341
5OO	Br	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1nc(C)cnc1C(F)(F)C(F)F</chem>	610.2016
5PP	F ₃ CO-	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1nc(C)cnc1C(F)(F)C(F)F</chem>	616.2746
5QQ	F ₃ C-	<chem>CH3CH2Oc1nc(C)c(O)cc1</chem>	<chem>Cc1nc(C)cnc1C(F)(F)C(F)F</chem>	600.2788

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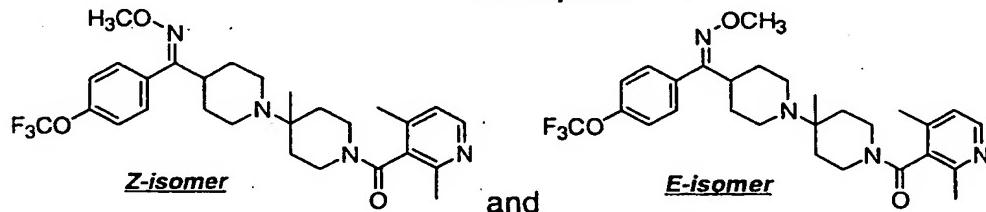
5RR	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		593.2131
5SS	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		590.1995
5TT	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		627.1729
5UU	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		556.218
5VV	Br	$\text{H}_3\text{CO}-\overset{\sim}{\text{N}}-\text{C}-$		542.2002
5WW	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		555.2336
5XX	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		655.287
5YY	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		566.2407
5ZZ	Br	$\text{H}_3\text{CO}-\overset{\sim}{\text{N}}-\text{C}-$		603.2349
5AB	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		617.2488
5AC	Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\sim}{\text{N}}-\text{C}-$		640.2868

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Additional data for compounds of Example 5:

Ex.	$^1\text{H-NMR}$ (300 MHz $^1\text{H NMR}$ (CDCl_3))
5J	7.50 (d, 2H), 7.15 -6.95 (m, 5H), 4.15 (m, 1H), 3.80 (s, 3H), 3.45 (s, 3H), 3.25 (s, 3H), 3.00 (m, 2H), 2.24 (s, 3H), 2.25 (s, 3H), 2.10 (m, 2H), 1.80- 1.50 (m, 7H), 0.92 (s, 3H)
5L	8.95 (s, 1H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 4.24 (m, 1H), 3.81 (s, 3H), 3.98 (m, 2H), 2.75-3.00 (m, 3H), 2.48 (s, 3H), 2.45 (s, 3H), 1.99 -2.20 (m, 4H), 1.73 (m, 3H), 1.20-1.62 (m, 4H), 0.94 (s, 3H)
5N	8.92 (s, 1H), 7.45 (d, $J = 9.0$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 4.21 (m, 1H), 4.02 (q, $J = 6.9$ Hz, 2H), 3.98 (m, 2H), 2.75-2.92 (m, 3H), 2.46 (s, 3H), 2.41 (s, 3H), 1.90 -2.20 (m, 4H), 1.73 (m, 3H), 1.27-1.62 (m, 4H), 1.15 (t, $J = 8.1$ Hz, 3H), 0.93 (s, 3H)

Example 6



- 5 A) Preparation of intermediate **27** (Scheme 8 ($R^1 = \text{CH}_3$)).
 - 1) **23** (40.0 g, 0.203 mol) is vigorously stirred in EtOAc (200 ml) and concentrated aqueous HCl (80 ml) for 1.5 h. The solution is concentrated, diluted with Et_2O (300 ml) and H_2O (150 ml), the aqueous layer is separated and the organic layer is extracted once with H_2O (20 ml).
- 10 Combined aqueous layers are concentrated and the residue is dried 24 h under high vacuum to provide 26.7 g (84%) of a white solid. To this hydrochloride and *N*-*tert*-butoxycarbonyl-4-piperidone (43.8 g, 0.22 mol) in anhydrous $\text{ClCH}_2\text{CH}_2\text{Cl}$ (80 mL) with 4 Å molecular sieves, are successively added DBU (33.2 ml, 0.22 mol) and titanium(IV) isopropoxide (65.5 ml, 0.22 mol) at 0 °C, the reaction mixture is allowed to warm to RT and is stirred overnight at RT. The mixture is then cooled to 0 °C and diethylaluminum cyanide, 1 N in toluene (260 ml, 0.26 mol) is added with vigorous stirring. The reaction is allowed to warm to RT and stirred an additional 3 h, after which are added CH_2Cl_2 (300 ml), EtOAc (300 ml), and
- 15 Celite (50 g). The reaction mixture is cooled to 0 °C, water (40 ml) is added slowly with vigorous stirring and, after an additional 5 min. stirring at RT, the excess of water is quenched with Na_2SO_4 . The final mixture is then
- 20 Celite (50 g). The reaction mixture is cooled to 0 °C, water (40 ml) is added slowly with vigorous stirring and, after an additional 5 min. stirring at RT, the excess of water is quenched with Na_2SO_4 . The final mixture is then

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filtered over Celite, evaporated and subjected to flash chromatography over silica gel (eluting with Hexanes/EtOAc, 8:2), to provide 50.3 g (83%) of **24** as a colorless oil which solidifies upon standing.

- 2) To a solution of **24** (27.7 g, 90.6 mmol) in anhydrous THF (200 mL) at 0 °C is slowly added CH₃MgBr 3 M in Et₂O (91 ml, 3 equiv.) with vigorous stirring. After the addition, the reaction is allowed to warm to RT and stirred 3 h. The reaction is then poured into aqueous saturated NH₄Cl, extracted with Et₂O (4 times), washed with brine, dried over Na₂SO₄, and concentrated to give 27.1 g (100%) of **25** as a colorless oil.
- 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 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7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 9935 9940 9945 9950 9955 9960 9965 9970 9975 9980 9985 9990 9995 9999

- 2) To a solution of the product of step 1 (8.85 g, 39.3 mmol) in CH₂Cl₂ (100 ml) at 0 °C is added Dess-Martin periodinane (19.70 g, 2.5 equiv.) and the reaction mixture is stirred 2 h at RT. An additional 8.0 g of Dess-Martin periodinane is added and the reaction is stirred for an additional
- 5 4 h. The solution is poured into a 1:1 mixture of aqueous saturated NaHCO₃ and aqueous saturated Na₂S₂O₃ (200 ml), stirred 10 min, extracted with CH₂Cl₂, and dried over Na₂SO₄. The residue obtained after concentration of the solvents is purified by flash chromatography over silica gel (eluting with hexanes/EtOAc, 7:3) to yield 5.48 g (63%) of the ketone as
- 10 a yellow oil.
- 3) A solution of the product of step 2 (2.85 g, 6.05 mmol), HONH₂·HCl (2.08 g, 30 mmol), and AcONa (2.46 g, 30 mmol) in EtOH (50 mL) is heated at reflux under N₂ for 4 h. After evaporation of the solvent, the residue is taken up in aqueous 0.1 N NaOH and extracted with CH₂Cl₂.
- 15 The residue obtained after evaporation of the solvents is subjected to flash chromatography over silica gel, to afford first the E-hydroxime (eluting with CH₂Cl₂/EtOAc, 7:3; 0.84 g; 29%), then the Z-hydroxime (eluting with CH₂Cl₂/EtOAc 1:1; 1.10 g; 37%), both products as white solids.
- 4) To a suspension of Z-hydroxime (0.89 g, 1.84 mmol) in anhydrous
- 20 DMF (5 ml) is slowly added KHMDA 0.5 N in toluene (4.0 ml, 2.02 mmol) at 0 °C, leading to the appearance of a yellow solution. After 2 min. at this temperature, dimethylsulfate (350 µl, 3.7 mmol) is slowly added and the solution is allowed to warm to RT and stirred 1 h. The mixture is poured into aqueous 0.1 N NaOH, extracted with CH₂Cl₂, and dried over Na₂SO₄.
- 25 The residue obtained after concentration of the solvents is purified by flash chromatography over silica gel (eluting with hexanes/EtOAc, 75:25) to afford 0.55 g (62%) of the Z-methoxime as a slightly yellow oil.
- 5) A solution of Z-methoxime (0.59 g, 1.18 mmol) in anhydrous CH₂Cl₂ (6 ml) and TFA (3 ml) is stirred 1 h at RT. After concentration, the residue
- 30 is taken up in aqueous 1 N NaOH, extracted with CH₂Cl₂, dried over Na₂SO₄ and concentrated to give 0.47 g (100%) of the free amine as a white foam.
- 6) A solution of the product of step 5 (470 mg, 1.18 mmol), 2,4-dimethylnicotinic acid (220 mg, 1.45 mmol), DEC (280 mg, 1.45 mmol),
- 35 HOBT (243 mg, 1.80 mmol) and N-methylmorpholine (0.33 ml, 3.0 mmol) in anhydrous DMF is stirred 14 h. After concentration, the residue is taken up in aqueous 0.1 N NaOH, extracted with CH₂Cl₂, and dried over Na₂SO₄. The residue obtained after concentration of the solvent is purified by flash

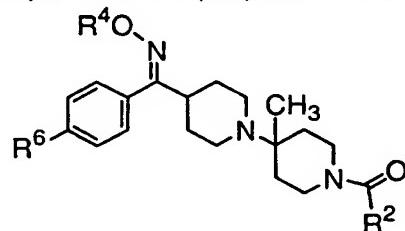
- 48 -

chromatography over silica gel (eluting with $\text{CH}_2\text{Cl}_2/\text{acetone}$, 7:3 to 1:1) to afford 640 mg (100%) of a colorless oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.35 (d, $J = 7.8$ Hz, 1H), 7.25 (AB system, 4H), 6.98 (d, $J = 7.8$ Hz, 1H), 4.22 (m, 1H), 3.82 (s, 3H), 3.43 (m, 1H), 3.33 (m, 1H), 2.99 (m, 2H), 2.85 (m, 1H), 2.49 (s, 3H, atropisomer a) and 2.51 (s, 3H, atropisomer b), 2.26 (s, 3H, atropisomer a) and 2.28 (s, 3H, atropisomer b), 1.95-2.21 (m, 3H), 1.20-1.90 (m, 7H), 0.92 (s, 3H).
 HRMS ($M+\text{H}^+$) 533.2747.

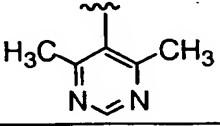
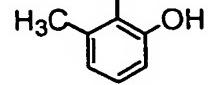
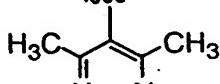
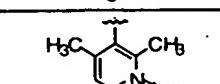
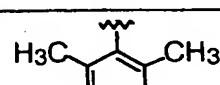
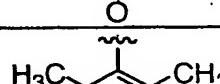
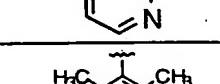
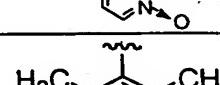
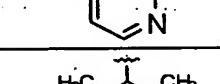
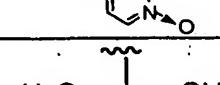
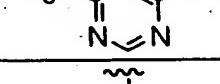
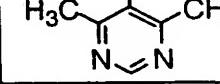
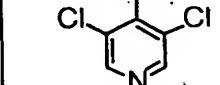
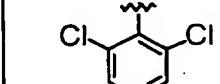
Following steps B-4, B-5, and B-6 using the E-oxime yields the corresponding E-methoxime product.

The following compounds are prepared via similar procedures:

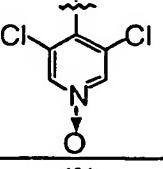
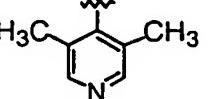
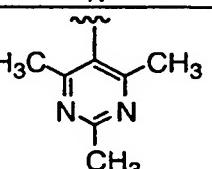
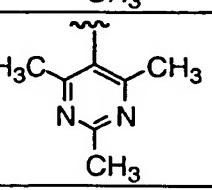
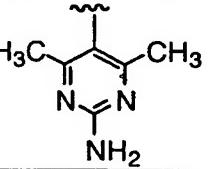


wherein R^4 , R^6 and R^2 are as defined in the table:

Ex.	R^6	R^4	R^2	HRMS ($M+\text{H}^+$) found
6A	Br	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	554.3000
6B	Br	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	555.2335
6C	Br	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{OH}$	556.2175
6D	Br	$\text{H}_3\text{CO}-\text{CH}_2-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	571.2284
6E	Br	$\text{H}_3\text{CO}-\text{CH}_2-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	570.2331
6F	Br		$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	569.1000
6G	$\text{F}_3\text{CO}-$	$\text{F}_3\text{C}-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	601.2628
6H	$\text{F}_3\text{CO}-$	$\text{F}_3\text{C}-\text{CH}_2-$	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_3$	617.2549

6I	$\text{F}_3\text{CO}-$	-CH ₃		534.2708
6J	$\text{F}_3\text{CO}-$		602.2465	
6K	$\text{F}_3\text{CO}-$		602.2579	
6L	$\text{F}_3\text{CO}-$		589.3013	
6M	Cl	CH ₃ CH ₂ -		513.2633
6N	Cl	CH ₃ -		483.2516
6O	$\text{F}_3\text{C}-$	CH ₃ -		533.2758
6P	Cl	CH ₃ CH ₂ -		497.2683
6Q	Cl	CH ₃ CH ₂ -		513.2642
6R	Cl	CH ₃ CH ₂ -		498.2633
6S	$\text{F}_3\text{C}-$	CH ₃ -		518.2749
6T	Cl	CH ₃ CH ₂ -		537.1603
6U	$\text{F}_3\text{C}-$	CH ₃ -		557.1680
6V	$\text{F}_3\text{C}-$	CH ₃ CH ₂ -		571.1838

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6W	Cl	CH ₃ CH ₂ -		555.8401
6X	Cl	CH ₃ CH ₂ -		497.2682
6Y	F ₃ CO-	CH ₃ -		548.2853
6Z	F ₃ CO-	CH ₃ CH ₂ -		562.3017
6AA	F ₃ CO-	CH ₃ CH ₂ -		563.2939

Additional data for compounds of Example 6:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
6F	8.31 (d, 1H), 7.51 (d, 2H), 7.10 (d, 2H), 6.95 (d, 2H), 4.20 (m, 2H), 3.40 (d, 2H), 3.30 (m, 2H), 3.35 (m, 3H), 2.80-3.05 (m, 5H), 2.45 (d, 3H), 2.25 (d, 3H), 1.25-2.20 (m, 10H), 0.50 (m, 2 H), 0.22 (m, 2H), 0.90 (s, 3H)
6G	8.34 (d, J = 5.1 Hz, 1H), 7.24 (br s, 4H), 6.96 (d, J = 5.1 Hz, 1H), 4.33 (q, J = 8.6 Hz, 2H), 4.13 (m, 1H), 3.45 (m, 1H), 3.30 (m, 1H), 2.98 (m, 2H), 2.82 (m, 1H), 2.46 and 2.49 (s, 3H), 2.41 (m, 1H), 2.24 and 2.27 (s, 3H), 2.10 (m, 2H), 1.96 (m, 1H), 1.15-1.90 (m, 7H), 0.92 (s, 3H)
6I	8.92 (s, 1H), 7.23 (br s, 4H), 4.11 (m, 1H), 3.79 (s, 3H), 3.30-3.45 (m, 2H), 2.97 (m, 2H), 2.81 (m, 1H), 2.45 and 2.42 (s, 6H), 2.40 (m, 1H), 1.90-2.20 (m, 3H), 1.15-1.90 (m, 7H), 0.92 (s, 3H)

Example 7

Alternate synthesis of the compounds of Example 6.

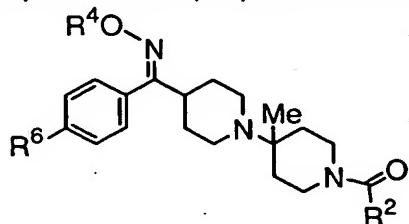
- 5 1) The product of Example 6, step B-2 (566 mg, 1.20 mmol) is treated with H₃CONH₂·HCl using conditions similar to those shown in Example 6,

step B-3. The resulting crude mixture of Z- and E-methoximes is separated on a preparative silica gel TLC plate (eluting with hexanes/ EtOAc, 80:20) to afford, in order of elution, first the E-methoxime (175 mg; 29%), then the Z-methoxime (175 mg; 29%), both products as oils.

- 5 2) The Z-methoxime (75 mg; 0.15 mmol) of step 1 is deprotected following conditions similar to those shown in Example 6, step B-5 and the resulting free amine (46 mg) is directly subjected to amidation with 2,4-dimethylnicotinic acid using conditions similar to those shown in Example 6, step B-6 to yield 50 mg (82%) of a colorless oil.

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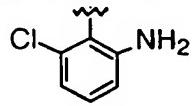
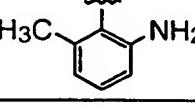
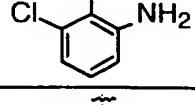
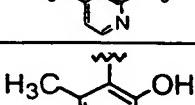
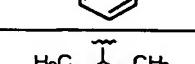
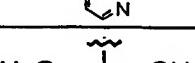
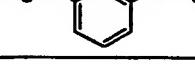
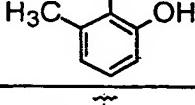
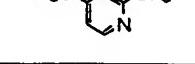
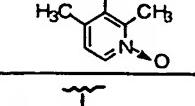
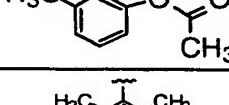
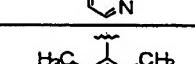
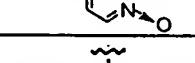
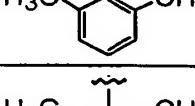
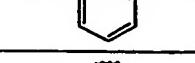
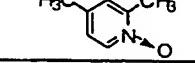
The following compounds are prepared via similar procedures:



wherein R⁴, R⁶ and R² are as defined in the table:

Ex.	R ⁶	R ⁴	R ²	HRMS (MH ⁺) found
7A	F ₃ CO-	CH ₃ -		532.2795
7B	F ₃ CO-	CH ₃ -		553.2192
7C	F ₃ CO-	CH ₃ -		533.2730
7D	F ₃ CO-	CH ₃ CH ₂ -		546.2940
7E	F ₃ C-	CH ₃ -		516.2833
7F	F ₃ CO-	CH ₃ -		534.2571
7G (E isomer)	F ₃ C-	CH ₃ -		537.2234

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7H	F ₃ C-	CH ₃ -		537.2234
7I	F ₃ C-	CH ₃ -		537.2234
7J	F ₃ CO-	CH ₃ CH ₂ -		567.2362
7K	F ₃ C-	CH ₃ -		517.2812
7L	F ₃ C-	CH ₃ CH ₂ -		532.2787
7M	F ₃ CO-	CH ₃ CH ₂ -		547.2888
7N	F ₃ CO-			572.3093
7O	F ₃ CO-	CH ₃ CH ₂ -		548.2732
7P (E isomer)	F ₃ C-	CH ₃ -		517.2831
7Q	F ₃ CO-	CH ₃ -		549.2686
7R	F ₃ CO-	CH ₃ CH ₂ -		590.2854
7S	F ₃ C-	CH ₃ CH ₂ -		531.1002
7T	F ₃ C-	CH ₃ CH ₂ -		547.1348
7U (E isomer)	F ₃ CO-	CH ₃ -		532.2784
7V	F ₃ CO-			576.3049
7W	F ₃ CO-	CH ₃ CH ₂ -		563.2855

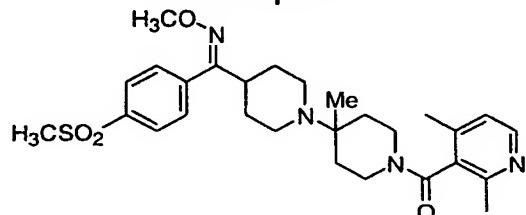
- 53 -

7X	F ₃ CO-			573.3052
7Y	F ₃ CO-			574.2889
7Z	F ₃ CO-	CF ₃ CH ₂ -		641.1537
7AA	F ₃ CO-	CH ₃ -		573.1638
7BB	F ₃ CO-	CH ₃ CH ₂ -		587.1821
7CC	F ₃ CO-	CH ₃ CH ₂ -		548.2861
7DD	F ₃ CO-	CH ₃ -		589.1610
7EE	F ₃ CO-	CH ₃ CH ₂ -		603.1748
7FF	F ₃ CO-	CH ₃ (CH ₂) ₂ -		562.3030
7GG	F ₃ CO-	CH ₃ (CH ₂) ₂ -		617.1918
7HH	F ₃ CO-	CH ₃ (CH ₂) ₂ -		577.3019

Additional data for compounds of Example 7:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
7H	7.55 (d, 2H), 7.30 (d, 2H), 7.15 (t, 1H), 6.75 (d, 1H), 6.60 (d, 1H), 4.25 (m, 2H), 3.80 (s, 3H), 3.40 (m, 2H), 2.80-3.20 (m, 3H), 2.40 (m, 1H), 1.40-2.20 (m, 13H), 0.90 (s, 3H)

7K	8.31 (d, 1H), 7.61 (d, 2H), 7.31 (d, 2H), 6.95 (d, 2H), 4.30 (m, 2H), 3.80 (3, 2H), 3.20-3.50 (m, 2H), 2.75-3.05 (m, 3H), 2.45 (d, 3H), 2.25 (d, 3H), 1.45-2.20 (m, 11H), 0.92 (s, 3H)
7Q	8.11 (d, $J = 6.8$ Hz, 1H), 7.25 (br s, 4H), 6.94 (d, $J = 6.8$ Hz, 1H), 4.16 (m, 1H), 3.75 (s, 3H), 3.20-3.45 (m, 2H), 2.85-3.00 (m, 3H), 2.41 (d, $J = 11.6$ Hz, 3H), 2.45 (m, 1H), 2.20 (d, $J = 11.6$ Hz, 3H), 1.85-2.20 (m, 3H), 1.15-1.85 (m, 7H), 0.88 (s, 3H)
7R	7.13-7.30 (m, 5H), 7.14 (m, 1H), 6.95 (m, 1H), 4.13 (m, 1H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.15-3.50 (m, 2H), 2.86-3.10 (m, 2H), 2.80 (m, 1H), 2.39 (m, 1H), 2.15-2.30 (m, 6H), 1.85-2.15 (m, 3H), 1.10-1.85 (m, 7H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.88 (br s, 3H)
7S	8.31 (d, 1H), 7.61 (d, 2H), 7.32 (d, 2H), 6.95 (d, 2H), 4.25 (m, 2H), 4.05 (q, 2H), 3.20-3.50 (m, 2H), 2.80-3.15 (m, 3H), 2.45 (d, 3H), 2.25 (d, 3H), 1.45-2.20 (m, 9H), 1.20 (t, 3H), 0.90 (s, 3H)

Example 8

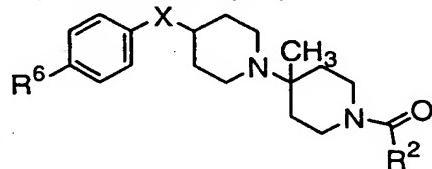
- 1) To a stirred solution of the product of Example 5, step 8 (0.500 g, 5 mmol) in DMF (25 ml) is added sodium methylmercaptide (0.113 g, 1.62 mmol) and the mixture is heated to 70° C for 12 h. The reaction mixture is then cooled to RT, diluted with Et₂O, washed with brine, dried and concentrated to yield 0.437 g (97%) of sulfide.
- 2) A solution of the product of step 1 (1.00 g; 2.31 mmol), H₃CONH₂·HCl (3.80 g, 46.2 mmol), and AcONa (3.79 g, 46.2 mmol) in EtOH (30 ml) is heated at reflux under N₂ for 4 h. After evaporation of the solvent, the residue is taken up in aqueous 0.1 N NaOH and extracted with CH₂Cl₂. The residue obtained after evaporation of the solvents is subjected to flash chromatography over silica gel, to afford first the E-oxime (eluting Et₂O/CH₂Cl₂, 1:4; 0.45 g; 24%), then the Z-oxime (0.25 g, 15%).
- 3) To a solution of Z-oxime (0.250 g, 0.543 mmol) of step 2 in CH₃OH (5 ml) at 0° C is added oxone (1.00 g, 1.627 mmol in 5 ml of CH₃OH) and the mixture is stirred at 0°C for 4 h. The reaction is then quenched with

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10% NaOH, concentrated, poured into water (10 ml) and extracted with CH₂Cl₂, dried and concentrated to yield 0.220 g (82%) of sulfone.

- 4) To a stirred solution of the product of step 3 (0.300 g, 0.608 mmol) in CH₂Cl₂ (5 ml) is added TFA(1 ml) and the mixture is stirred at RT for 2 h.
- 5 The reaction mixture is concentrated, poured into 10% NaOH and extracted with CH₂Cl₂. The combined extracts are dried and concentrated to afford 0.240 g (100%) of amine.
- 5) To stirred solution of the product of step 4 (0.45 g, 0.114 mmol) in CH₂Cl₂ is added 2,6-dimethylnicotinic acid (0.26 g, 0.172 mmol), DEC (0.33 g, 0.172 mmol), N,N,N-diisopropylethylamine (DIPEA) (0.2 ml) and HOBT (0.24g, 0.172 mmol) and the mixture is stirred for 12 h at RT. The reaction mixture is quenched with NaHCO₃, extracted with CH₂Cl₂, dried, concentrated and purified by preparative chromatography (20% EtOH/EtOAc) to afford 0.046 g (76%) of Z-oxime amide.
- 15 300 MHz ¹H NMR (CDCl₃) δ 8.32 (d, 1H), 7.95 (d, 2H), 7.40 (d, 2H), 6.95 (d, 1H), 4.20 (m, 1H), 3.82 (s, 3H), 3.30-3.45 (m, 3H), 3.10 (s, 3H), 2.80-3.00 (m, 3H), 2.50 (d, 2H), 2.25 (d, 2H), 1.30- 2.20 (m, 12H), 0.92 (s, 3H).

The following compounds were prepared in a similar manner:

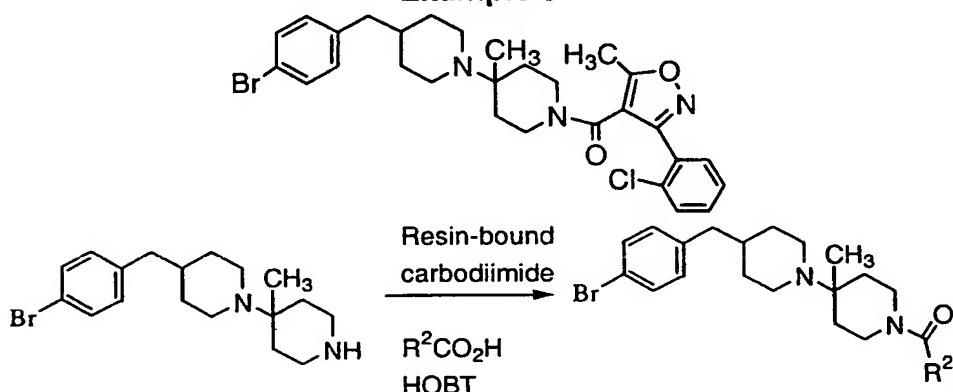


- 20 wherein X, R⁶ and R² are as defined in the table:

Ex.	R ⁶	X	R ²	HRMS (M ⁺) found
8A (mixture E/Z)				526.2753
8B				547.2135
8C	Br			549.2133
8D				541.2849
8E				557.2798

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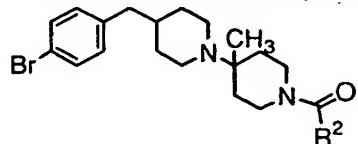
8F				543.2641
8G				527.2692
8H				532.2895
8I				542.2796

Example 9

- 5 Dissolve the starting amine (2.0 g , 5.7 mmol) in CHCl₃ (57 ml; = Stock solution A ~ 0.1M). Add 430 μ l of stock solution A (0.043 mmol) to a slurry of 0.25 g (~ 0.22 mmol) of resin bound cardodiimide (prepared by reacting Argopore-Cl resin with 1-(3-dimethylaminopropyl)3-ethyl carbodiimide in DMF at 100 C) in DMF (2 ml) in a polyethylene SPE cartridge. To this mixture add 0.12 ml of a 1M solution of 5-methyl-3-[2-chlorophenyl]isoxazole-4-carboxylic acid in DMF (0.12 mmol), HOBT (86 μ l of a 0.5M solution in DMF) and DMAP (25 μ l of a 0.05M solution in DMF). Shake this mixture for 14 h, filter and add 0.3 g of Amberlyst-15 resin (~ 1.5 mmol) to the filtrate. Shake for 1 to 2 h, filter and wash the resin twice with each of the following solvents: THF, CH₂Cl₂ and CH₃OH, then wash with THF and CH₂Cl₂. Treat the resin with 2M NH₃ in CH₃OH (1 time for 30 min, and 1 time for 5 min.). Combine and concentrate the filtrates under reduced pressure to afford the title compound. LCMS found MH⁺= 570, 572 (calculated MW 571); TLC R_f = 0.45 (CH₂Cl₂/CH₃OH/ NH₄OH (95/5/0.5)).
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- 15
- 20

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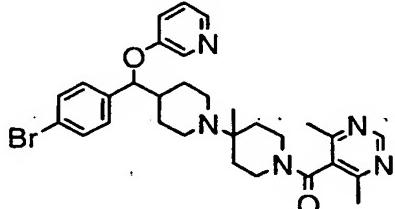
Using a similar procedure, the following compounds were prepared



wherein R² is as defined in the table:

Ex.	R ²	Data	TLC R _f values
9A		LCMS: MH ⁺ = 538.1 R _t = 6.27 min	0.58
9B		MS m/e = 475.2, 477.2 (Electrospray)	
9C		LCMS: MH ⁺ = 606	0.57
9D		LCMS: MH ⁺ = 507.1 R _t = 6.39 min	0.49
9E		LCMS: MH ⁺ = 497.1 R _t = 6.32 min	0.48

Example 10



5

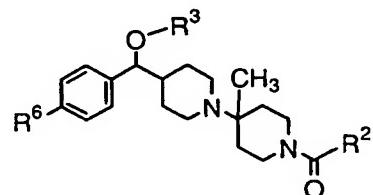
Step 1: To a solution of alcohol **39ab** (406 mg; 0.87 mmol), 3-hydroxy-pyridine (95.1 mg; 1 mmol) and PPh₃ (262 mg; 1 mmol) in anhydrous THF (2 ml) at 0 °C was added diethylazodicarboxylate (160 ml; 1 mmol) and the mixture was allowed to warm to RT overnight. The reaction was poured into 5% aqueous NaHCO₃, extracted with CH₂Cl₂, and dried over Na₂SO₄. After concentration of the solvents, the resulting oil was purified by flash chromatography over silica gel (eluting CH₂Cl₂/CH₃OH 97:3 to 95:5) to afford the desired compound (290 mg; 61%), as an oil.

Step 2: Removal of the Boc-protecting group of the product of step 1 (290 mg; 0.53 mmol) proceeded as in Example 2 to obtain the desired amine (210 mg; 89%), as a white foam.

Step 3: The amine of step 2 (50 mg; 0.11 mmol) was coupled with 4,6-dimethylpyrimidine-5-carboxylic acid following the conditions described in Example 2 to obtain the title compound (32 mg; 49%) as a colorless oil:

1H-NMR (300 MHz, CDCl₃) δ 8.91 (s, 1H), 8.20 (br s, 1H), 8.10 (d, J = 4.5 Hz, 1H), 7.43 (br d, J = 8.4 Hz, 2H), 7.14 (br d, J = 8.4 Hz, 2H), 6.95-7.10 (m, 2H), 4.75 (br d, J = 6.8 Hz, 1H), 4.15 (m, 1H), 3.44 (m, 1H), 3.33 (m, 1H), 2.95 (m, 2H), 2.79 (m, 1H), 2.42 and 2.44 (s, 3H), 1.85-2.15 (m, 3H), 1.65-1.85 (m, 2H), 1.15-1.50 (m, 5H), 0.90 (s, 3H); HRMS (MH⁺) 578.2115.

10 Using similar procedures, compounds of the following structure were prepared



wherein R³, R⁶ and R² are as defined in the table:

Ex.	R ⁶	R ³	R ²	HRMS (MH ⁺) found
10A	CH ₃ SO ₂ -			592.2848
10B	Br			577.2166
10C	Br			595.2078
10D	F			517.2992
10E	F			516.3031
10F	F			532.2981
10G	Br			595.2072
10H	Cl			567.2308

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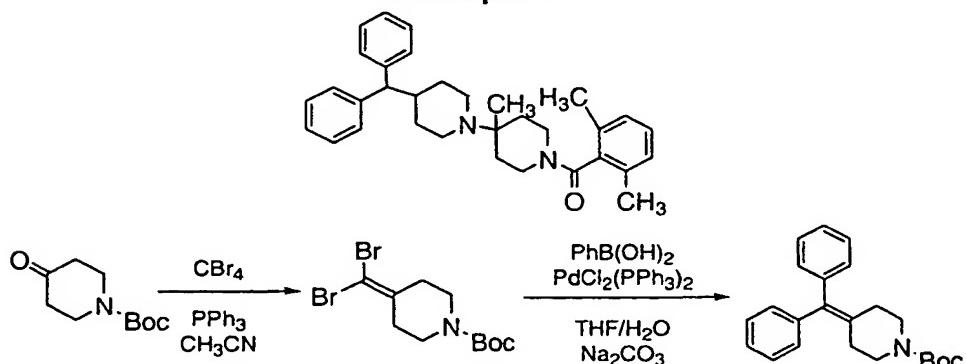
10I	F_3C^-			582.2955
10J	CH_3SO_2^-			577.2853
10K	CH_3SO_2^-			595.2764
10L	F_3CO^-			601.2817
10M	F_3CO^-			617.2514
10N	CH_3SO_2^-			611.2460
10O	CH_3SO_2^-			595.2749
10P	F_3C^-			597.2951
10Q	F_3CO^-			583.2905
10R	F_3CO^-			598.2903
10S	F_3C^-			601.2556
10T	F_3C^-			585.2559
10U	F_3CO^-			584.2860

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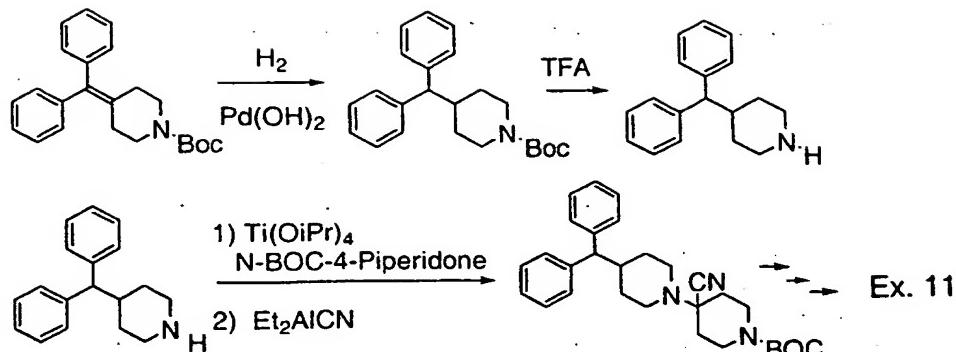
Additional data for compounds of Example 10:

Ex.	¹ H-NMR (300 MHz ¹ H NMR (CDCl ₃))
10C	8.95 (s, 1H), 7.46 (br d, <i>J</i> = 8.4 Hz, 2H), 7.17 (br d, <i>J</i> = 8.4 Hz, 2H), 6.86 (t, <i>J</i> = 9 Hz, 2H), 6.70-6.72 (m, 2H), 4.69 (br d, <i>J</i> = 6.4 Hz, 1H), 4.19 (m, 1H), 3.47 (m, 1H), 3.37 (m, 1H), 2.99 (m, 2H), 2.82 (m, 1H), 2.47 and 2.50 (s, 3H), 1.90-2.15 (m, 3H), 1.65-1.90 (m, 2H), 1.20-1.50 (m, 5H), 0.93 (s, 3H)
10F	8.17 (d, <i>J</i> = 6.8 Hz, 1H), 7.28 (m, 2H), 7.18 (t, <i>J</i> = 7.5 Hz, 1H), 6.95-7.10 (m, 3H), 6.87 (t, <i>J</i> = 7.5 Hz, 1H), 6.80 (d, <i>J</i> = 7.5 Hz, 2H), 4.80 (d, <i>J</i> = 6.8 Hz, 1H), 4.17 (m, 1H), 3.25-3.50 (m, 2H), 2.99 (m, 2H), 2.80 (m, 1H), 2.43 (br s, 3H), 2.24 (br s, 3H), 1.65-2.20 (m, 5H), 1.15-1.50 (m, 5H), 0.90 (s, 3H)
10H	8.95 (s, 1H), 7.32 (br d, <i>J</i> = 8.4 Hz, 2H), 7.23 (br d, <i>J</i> = 8.4 Hz, 2H), 7.08 (t, <i>J</i> = 8.1 Hz, 1H), 6.80-6.90 (m, 2H), 6.68 (m, 1H), 4.77 (br d, <i>J</i> = 6.8 Hz, 1H), 4.19 (m, 1H), 3.46 (m, 1H), 3.37 (m, 1H), 3.00 (m, 2H), 2.81 (m, 1H), 2.47 and 2.49 (s, 3H), 1.90-2.15 (m, 3H), 1.65-1.90 (m, 2H), 1.20-1.50 (m, 5H), 0.93 (s, 3H)
10K	8.81 (s, 1H), 7.78 (d, <i>J</i> = 8.4 Hz, 2H), 7.53 (m, 1H), 7.47 (d, <i>J</i> = 8.4 Hz, 2H), 6.90 (m, 1H), 6.74 (m, 1H), 6.59 (m, 1H), 4.83 (d, <i>J</i> = 6.8 Hz, 1H), 4.08 (m, 1H), 3.20-3.40 (m, 2H), 2.70-3.00 (m, 3H), 2.35 (br s, 3H), 1.65-2.15 (m, 5H), 1.15-1.50 (m, 5H), 0.87 (s, 3H)
10L	8.33 (d, <i>J</i> = 5.1 Hz, 1H), 7.99 (dd, <i>J</i> = 4.8 and 1.8 Hz, 1H), 7.86 (d, <i>J</i> = 8.4 Hz, 2H), 7.56 (d, <i>J</i> = 8.4 Hz, 2H), 7.53 (m, 1H), 6.96 (d, <i>J</i> = 6.4 Hz, 1H), 6.75-6.85 (m, 2H), 4.15 (m, 1H), 3.45 (m, 1H), 3.30 (m, 1H), 3.02 (s, 3H), 2.99 (m, 2H), 2.79 (m, 1H), 2.47 and 2.48 (s, 3H), 2.45 (m, 1H), 2.25 and 2.26 (s, 3H), 1.65-2.15 (m, 5H), 1.15-1.55 (m, 5H), 0.90 (s, 3H)

Example 11



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- 1) N-Boc-4-piperidone (10 g, 50 mmol) and PPh_3 (53 g, 200 mmol) were taken up in CH_3CN (100 ml). The solution was cooled to 0 °C and CBr_4 (33 g, 100 mmol) was added to the solution at 0 °C. The solution was stirred at 0 °C for 15 min. and at 25 °C for 2 h. Et_2O (200 ml) was added, and the resulting mixture was filtered through a plug of SiO_2 .
- 5 Concentration gave a yellow solid. Purification via flash chromatography (9/1 hexanes/ Et_2O , SiO_2) gave 10 g (56 %) of the di-bromo product as a white solid.
- 10 2) A solution of the product of step 1 (1 g, 2.8 mmol), PhB(OH)_2 (1.2 g, 9.9 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (197 mg, 0.28 mmol), and Na_2CO_3 (897 mg, 8.5 mmol) were taken up in $\text{THF}/\text{H}_2\text{O}$ (4/1, 20 ml) and stirred at 65 °C under N_2 for 24 h. The solution was partitioned between EtOAc and H_2O , the aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and concentration gave a dark brown oil. Purification via flash chromatography (9/1 hexanes/ Et_2O , SiO_2) gave 941 mg (96 %) of the desired product as a white solid, m.p. = 152-153 °C.
- 15 3) A solution of the product of step 2 (500 mg, 1.4 mmol) and Pd(OH)_2 on carbon (100 mg, 20 wt % Pd (dry basis), 50 wt % H_2O) were taken up in CH_3OH (20 ml) and shaken in a Parr apparatus under H_2 (50 psi) for 15 h. The mixture was filtered and concentrated to give 501 mg (99 %) of the diphenylmethyl piperidine as a colorless oil.
- 20 4) TFA (1.4 ml) was added to a solution of the product of step 3 (500 mg, 1.4 mmol) in CH_2Cl_2 (15 ml). The solution was stirred at 25 °C for 23 h. The solution was concentrated and the residue partitioned between CH_2Cl_2 and 1 N NaOH . The aqueous layer was extracted with CH_2Cl_2 , the combined organic layers were dried over Na_2SO_4 , filtered and concentrated to obtain 349 mg (99 %) of the free amine as a yellow oil,

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m.p. (HCl) = decomp. above 220-230 °C. HRMS calc'd for C₁₈H₂₂N (MH⁺): 252.1752, Found: 252.1751.

5) A solution of the product of step 4 (349 mg, 1.4 mmol), N-Boc-4-piperidone 280 mg, 1.4 mmol), and Ti(O*i*Pr)₄ (0.42 ml, 1.4 mmol) were taken up CH₂Cl₂ (15 ml) under N₂. After stirring at 25 °C for 17 h, Et₂AlCN (2.8 mmol, 2.8 ml of 1.0 M in toluene) was added and the solution was stirred an additional 18 h at 25 °C. The solution was quenched with sat. NaHCO₃, diluted with EtOAc and filtered through Celite. The aqueous layer was extracted with EtOAc and the combined EtOAc layers were dried over Na₂SO₄. Filtration and concentration gave a yellow oil. Purification via preparative layer chromatography (3/1 hexanes/EtOAc, SiO₂) gave 430 mg (67 %) of the desired product as an oil.

10) A solution of the product of step 5 (430 mg, 0.94 mmol) in THF (20 ml) was cooled to 0 °C under N₂. CH₃MgBr (1.6 ml of 3.0 M in Et₂O, 4.7 mmol) was added at 0 °C and the solution stirred at 25 °C for 19 h. The reaction mixture was quenched with sat. NH₄Cl, diluted with CH₂Cl₂ and 1 N NaOH (check aqueous layer with pH paper, pH = 8-10). The layers were separated and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain 20) a yellow oil. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO₂) gave 275 mg (65 %) of the product as a yellow oil.

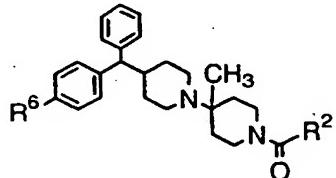
20) TFA (0.60 ml) was added to a solution of the product of step 6 (275 mg, 0.61 mmol) in CH₂Cl₂ (15 ml) and the solution was stirred at 25 °C for 18 h. The solution was concentrated and the residue was partitioned between CH₂Cl₂ and 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain 209 mg (99 %) of the amine as a yellow oil. HRMS calc'd for C₂₄H₃₃N₂ (MH⁺): 349.2644, Found: 349.2638.

30) A solution of the product of step 7 (50 mg, 0.14 mmol), 2,6-dimethylbenzoic acid (63 mg, 0.42 mmol), EDCI (54 mg, 0.28 mmol), HOBT (38 mg, 0.28 mmol), and iPr₂NEt (0.10 ml) were taken up in CH₂Cl₂ (3 ml). The solution was stirred at 25 °C for 18 h, then diluted with CH₂Cl₂ and washed with 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, and filtered and concentrated to give a yellow oil. Purification via preparative thin-layer chromatography (3/1 hexanes/EtOAc SiO₂) gave 47 mg (70 %) of the title

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compound as a colorless oil, m.p. (HCl salt) = 195-201 °C. HRMS calc'd for C₃₃H₄₁N₂O (MH⁺): 481.3219, Found: 481.3225.

Using similar procedures, compounds of the following structure were prepared

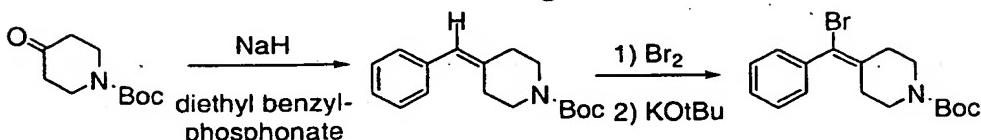
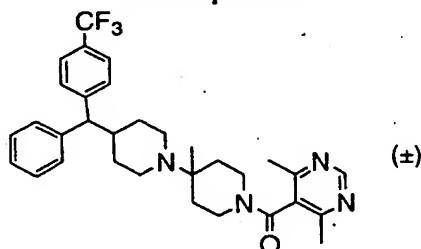


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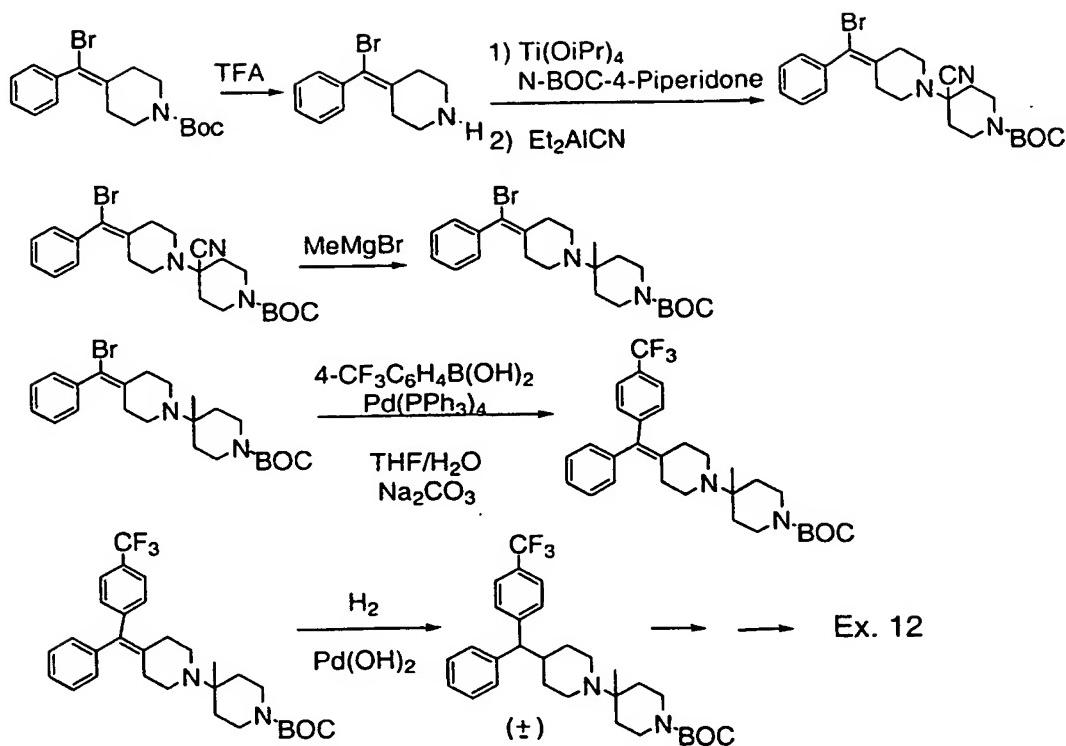
wherein R⁶ and R² are as defined in the table:

Ex.	R ⁶	R ²	HRMS (MH ⁺) found	M.p., °C (HCl salt)
11A	H		482.3156	201-207
11B	F ₃ CO-		565.3069	204-209
11C	H		482.3168	187-192
11D	F ₃ CO-		567.2957	175-181
11E	F ₃ CO-		582.2966	92-98
11F	F ₃ CO-		566.3020	175-181

Example 12



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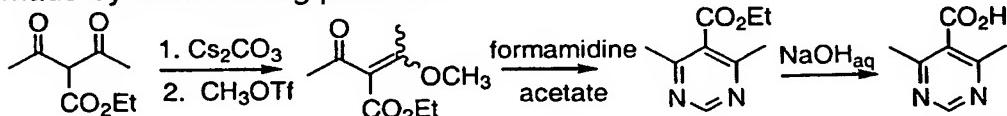
- 1) N-Boc-4-piperidone (10 g, 50 mmol) and diethyl benzylphosphonate (12.6g, 55 mmol) were taken up in dry THF (50 ml) under N₂. NaH (2.4 g, 60 mmol, 60 wt % in oil dispersion) was added to the solution at 25 °C.
- 5 The resulting mixture was heated at reflux for 3.5 h. The solution was partitioned between EtOAc and saturated NH₄Cl, the aqueous layer was extracted with EtOAc and the combined EtOAc layers were washed with brine and dried over MgSO₄. Filtration and concentration afforded a yellow oil. Purification via flash chromatography (10/1 hexanes/Et₂O, SiO₂) gave 9.85 g (72 %) of the desired compound as a solid, m.p. = 63-65 °C.
- 10 2) Bromine (1 ml, 20 mmol; dissolved in 10 ml CH₂Cl₂) was added dropwise to a CH₂Cl₂ (100 ml) solution of the product of step 1 (5.0 g, 18 mmol) at 0 °C. The solution was stirred at 0 °C for 15 min, then concentrated under reduced pressure. The crude product was taken up in tert-butanol/THF (4/1, 100 ml), and KOtBu (4.1 g, 36 mmol) was added to the solution in portions. The yellow mixture was stirred at 25 °C for 5h, then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated NH₄Cl, the aqueous layer was extracted with EtOAc, and the combined EtOAc layers were washed with brine and dried over MgSO₄. Filtration and concentration gave a yellow solid.
- 15 Purification via flash chromatography (7/1 hexanes/Et₂O, SiO₂) gave 5.2 g (81 %) of the desired product as a yellow solid. m.p. = 80-83 °C.
- 20

- 3) TFA (5.9 ml) was added to a solution of the product of step 2 (2.1 g, 5.9 mmol) in CH₂Cl₂ (25 ml). The solution was stirred at 25 °C for 5 h, concentrated and the residue was partitioned between CH₂Cl₂ and 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain 1.46 g (98 %) of the amine as an orange oil, m.p. (HCl salt) = decomp. above 185-195 °C. HRMS calc'd for C₁₂H₁₅BrN (MH⁺): 254.0367, Found: 254.0374.
- 4) A solution of the product of step 3 (1.4 g, 5.6 mmol), N-Boc-4-piperidone (1.1 g, 5.6 mmol), and Ti(O*i*Pr)₄ (1.7 ml, 5.6 mmol) were taken up in CH₂Cl₂ (30 ml) under N₂. After stirring at 25 °C for 18 h, Et₂ALCN (6.7 mmol, 6.7 ml, 1.0 M in toluene) was added to the solution and the solution was stirred an additional 18 h at 25 °C. The solution was quenched with sat. NaHCO₃, diluted with EtOAc and filtered through Celite. The aqueous layer was extracted with EtOAc and the combined EtOAc layers were dried over Na₂SO₄. Filtration and concentration gave a yellow oil. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO₂) gave 2.0 g (78 %) of the desired product as an off-white solid.
- 5) A solution of the product of step 4 (2.0 g, 4.3 mmol) in THF (30 ml) was cooled to 0 °C under N₂. CH₃MgBr (7.2 ml of 3.0 M in Et₂O, 21 mmol) was added to the solution at 0 °C. The solution was warmed to 25 °C and stirred at that temperature for 16 h. The reaction mixture was quenched with sat. NH₄Cl and diluted with CH₂Cl₂ and 1 N NaOH (check aqueous layer with pH paper, pH = 8-10). The layers were separated, the aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄. Filtration and concentration gave a yellow oil. Purification via flash chromatography (3/1 hexanes/EtOAc, SiO₂) gave 1.56 g (82 %) of the desired product as a yellow oil.
- 6) A solution of the product of step 5 (300 mg, 0.67 mmol), 4-CF₃C₆H₄B(OH)₂ (380 mg, 2 mmol), PdCl₂(PPh₃)₂ (50 mg, 0.067 mmol), and Na₂CO₃ (210 mg, 2 mmol) were taken up THF/H₂O (4/1, 15 ml) and stirred at 65 °C under N₂ for 18 h. The solution was partitioned between EtOAc and H₂O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and concentration gave a dark brown oil. Purification via flash chromatography (4/1 hexanes/EtOAc, SiO₂) gave 229 mg (67 %) of the desired product as a colorless oil.

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- 7) A solution of the product of step 6 (229 mg, 0.45 mmol) and Pd(OH)₂ on carbon (200 mg, 20 wt % Pd (dry basis), 50 wt % H₂O) were taken up in CH₃OH (35 ml) and shaken in a Parr apparatus under H₂ (50 psi) for 20 h. The mixture was filtered and concentrated to obtain 232 mg
 5 (100 %) of the (\pm)-product as a colorless foam. HRMS calc'd for C₃₀H₄₀O₂N₃ (MH⁺): 517.3042, Found: 517.3050.
- 8) TFA (0.45 ml) was added to a solution of the product of step 7 (235 mg, 0.45 mmol) in CH₂Cl₂ (15 ml). The solution was stirred at 25 °C for 24 h, then concentrated and the residue was partitioned between CH₂Cl₂ and
 10 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain 146 mg (78 %) of the (\pm)-amine as a yellow oil.
- 15 9) A solution of the product of step 8 (102 mg, 0.25 mmol), 4,6-dimethylpyrimidine-5-carboxylic acid (110 mg, 0.75 mmol), EDCI (96 mg, 0.50 mmol), HOBT (70 mg, 0.50 mmol), and iPr₂NEt (0.17 ml) was taken up in CH₂Cl₂ (3 ml). The solution was stirred at 25 °C for 18 h, then diluted with CH₂Cl₂ and washed with 1 N NaOH. The aqueous layer was extracted with CH₂Cl₂, the combined organic layers were dried over Na₂SO₄, filtered and concentrated to obtain a yellow oil. Purification via
 20 preparative thin-layer chromatography (1/1 acetone/hexanes SiO₂) gave 121 mg (88 %) of the title compound as a colorless oil, m.p. (HCl salt) = 186-191 °C. HRMS calc'd for C₃₂H₃₈N₄OF₃ (MH⁺): 551.2998, Found: 551.3012.

The 4,6-dimethylpyrimidine-5-carboxylic acid used in step 9 was
 25 made by the following process:



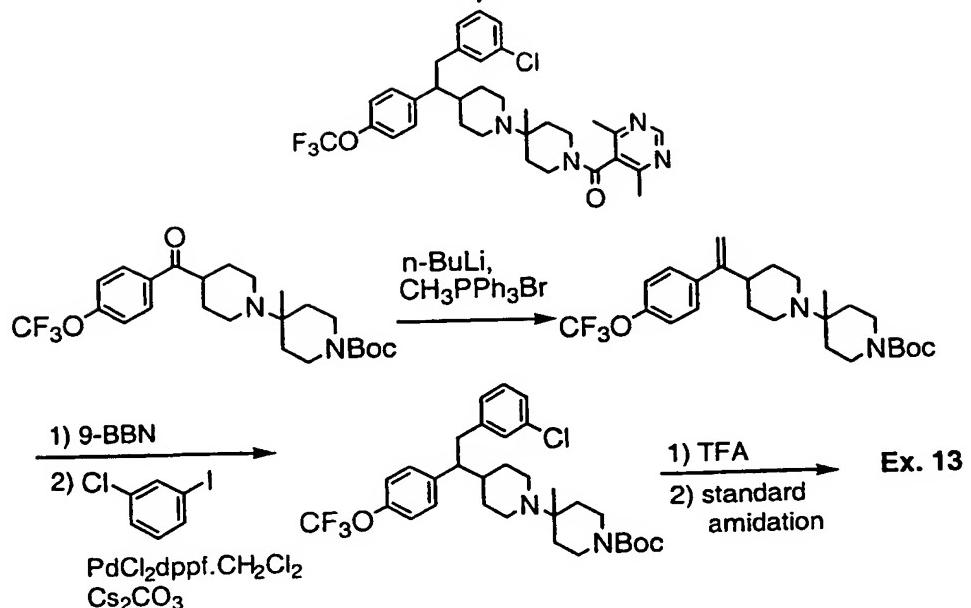
- Step 1: Ethyl diacetoacetate (93.4 g), Cs₂CO₃ (185 g) and CH₃CN (550 ml) were mixed together, using an overhead mechanical stirrer. CH₃CN (50 ml) was added and the resulting mixture was cooled to 0°C. Methyl trifluoromethane sulfonate (88.6 g) was added dropwise and after addition, the cooling bath was removed. The mixture was stirred for 1 h at RT, filtered, and the salts were washed with Et₂O (2 X 50 ml). The organic extracts were combined and Et₂O (300 ml) was added. The resulting mixture was filtered, the filter cake was washed with Et₂O (2 X 100 ml), the
 30 Et₂O extracts were combined and evaporated to half volume. The solution
 35 was cooled in an ice bath and washed once with cooled (0°C) 2 N NaOH

(pH = 11). The Et₂O layer was dried over MgSO₄, filtered and evaporated to give the desired product as a yellow liquid (64.7 g) in 65% yield, which was used directly in the next step.

- 5 Step 2: The product of step 1 (64.2 g), sodium ethoxide in ethanol (commercial solution; 21 wt%; 113 g) and formamidine acetate (36.2 g) were mixed together at RT. After refluxing for 4 h, the mixture was cooled to RT, the resulting precipitate was filtered off and the ethanol was removed under vacuum. The resulting liquid was partitioned between water and CH₂Cl₂ and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 ml). The CH₂Cl₂ extracts were dried over MgSO₄, filtered and evaporated to give a dark crude liquid (50.7 g) which was purified by silica gel chromatography (980 g; 4:1 hexanes:EtOAc as eluant). After evaporation of the appropriate fractions, the desired product (28.5 g) was isolated in 46% yield and used directly in the next step.
- 15 Step 3: The product of step 2 (28.1 g), NaOH (6.72 g), water (65 ml) and EtOH (130 ml) were mixed together at RT and heated at reflux for 1h. The resulting solution was cooled to RT and the volatile materials were removed in vacuo until a thick paste resulted. Water (20 ml) was added, the mixture was cooled to 0°C and conc. HCl (14.3 ml) was added dropwise with stirring. The resulting white precipitate was collected by filtration, washed with ice water (2 X 10 ml) and air dried with suction for 30 min. The resulting white solid was treated with toluene (2 x 20 ml); the solvent was removed in vacuo at 50°C and then dried under vacuum (1 mm Hg) for 18 h. The desired product (14.9 g) was isolated as a white solid in 63% yield, mp: 176-178°C. Elemental analysis of C₇H₈N₂O₂: calc'd C 55.26%, H 5.30%, N 18.41%; found: C 55.13%, H 5.44%, N 18.18%.

20 A second crop of product was isolated by evaporation of the aqueous filtrate (from above) to dryness and addition of water (20 ml). The resulting mixture was stirred at RT for 5 min, cooled in an ice bath and the precipitate formed was collected by filtration. The resulting solid was washed with ice water (2 X 5 ml) and dried as described above to give the product (4.68 g) as a cream colored solid to give a combined yield of 83%.

Example 13



Step 1: To a suspension of methyltriphenylphosphonium bromide (1.89 g; 4.80 mmol) in anhydrous THF (15 ml) at -40 °C is added n-BuLi 2.5 N in hexanes (2.12 ml; 5.3 mmol) via syringe. The reaction is allowed to warm to 0 °C, stirred 30 min at this temperature, and a solution of the product of Example 6, step B-2 (2.24 g; 4.8 mmol) is added. The solution is then allowed to warm to RT overnight, poured into CH₂Cl₂, and washed with

- 5 saturated NaHCO₃ then brine. The residue obtained after concentration of the organic layer is purified by flash chromatography over silica gel (eluting with CH₂Cl₂/EtOAc, 9:1) to afford 0.56 g (25%) of an oil.
- 10 Step 2: A solution of the product of step 1 (0.56 g; 1.2 mmol) and 9-BBN 0.5 N in THF (3 ml; 1.5 mmol) is refluxed 2 h under inert atmosphere. Part 15 of this solution (1.5 ml; 0.59 mmol of theoretical intermediate) is added to a mixture of 1-chloro-3-iodobenzene (88 µl; 0.71 mmol), PdCl₂dppf·CH₂Cl₂ (19.8 mg), triphenylarsine (24.1 mg) and Cs₂CO₃ (250 mg) in DMF (0.40 ml) and water (80 µl). The reaction is stirred 2 h at 60 °C and overnight at RT, poured into 5% aqueous NaHCO₃, and extracted with CH₂Cl₂. Combined 20 organic layers are dried over Na₂SO₄, concentrated, and purified by chromatography over silica gel (eluting with EtOAc/hexanes, 8:2) to provide 100 mg (29%) of an oil.

- 25 Step 3: The Boc-protecting group of the product of step 2 (100 mg; 0.17 mmol) was removed as in Example 2 to obtain the desired amine (70 mg; 86%). This amine (45 mg; 0.09 mmol) was coupled with 4,6-dimethyl-pyrimidine-5-carboxylic acid following the conditions described in Example

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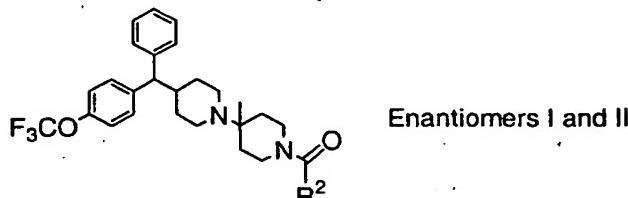
2 to obtain the title compound as a colorless oil (32 mg). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.93 (d, $J = 3.8$ Hz, 1H), 6.90-7.10 (m, 5H), 6.88 (br s, 1H), 6.71 (d, $J = 7$ Hz, 1H), 4.20 (m, 1H), 3.25-3.55 (m, 2H), 3.19 (m, 2H), 2.50-3.10 (m, 5H), 2.47 and 2.48 (s, 3H), 2.42 and 2.43 (s, 3H), 1.70-2.20 (m, 5H), 1.20-1.65 (m, 5H), 0.92 (s, 3H); HRMS (MH $^+$) 615.2722.

5 Using a similar procedure, the following compound was also prepared:

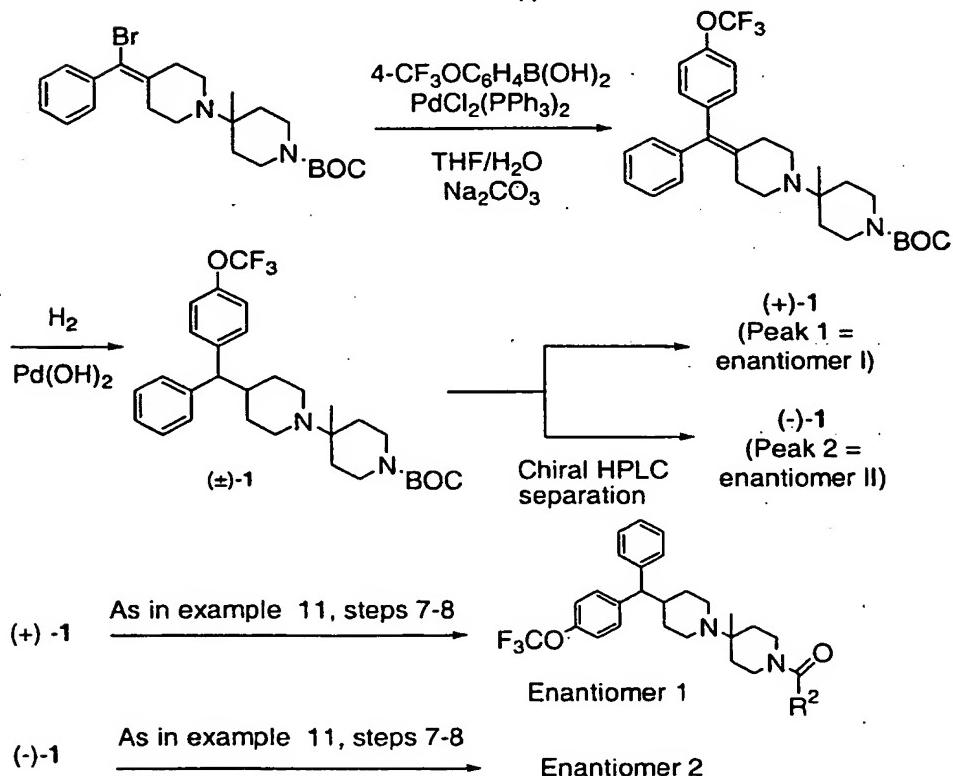


13A HRMS (MH $^+$) 599.3015

Example 14



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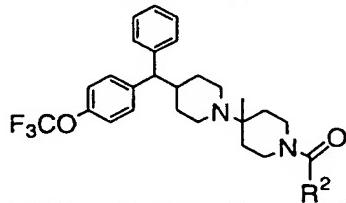
To prepare a compound wherein R^2 is 2,6-dimethylphenyl:

- 1) A solution of the product of step 5 in example 12 (300 mg, 0.67 mmol), $4\text{-CF}_3\text{OC}_6\text{H}_4\text{B}(\text{OH})_2$ (410 mg, 2 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (50 mg, 0.067

15 mmol), Na_2CO_3 (1.5 g, 11.5 mmol), H_2 (1 atm), $\text{Pd}(\text{OH})_2$ (100 mg), and H_2O (10 mL) was stirred at room temperature for 1 h. The reaction mixture was then purified by column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 9:1) to yield the title compound as a colorless oil (100 mg).

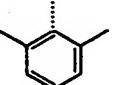
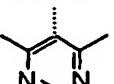
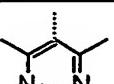
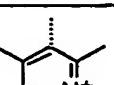
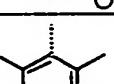
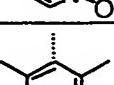
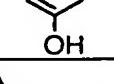
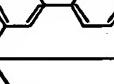
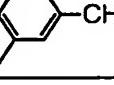
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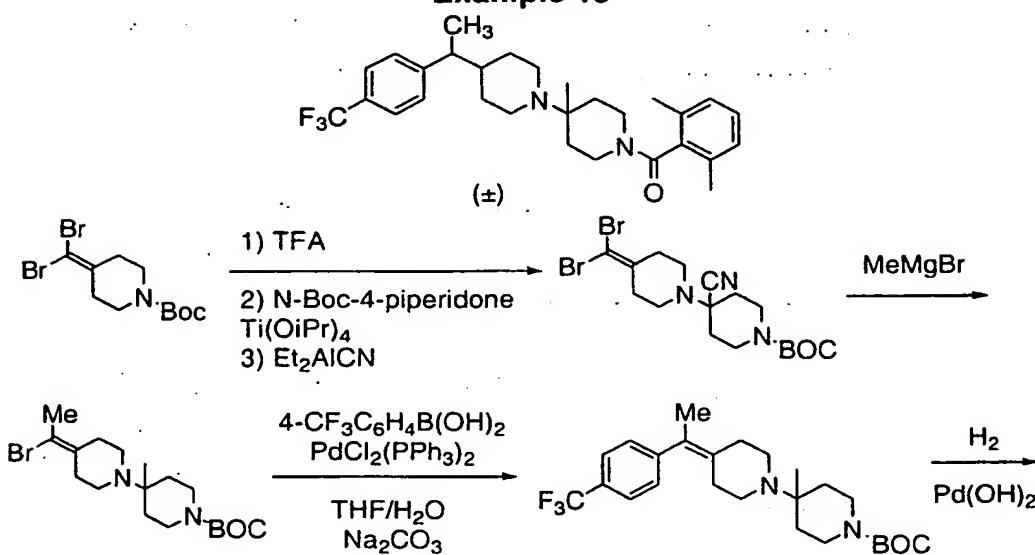
- mmol), and Na₂CO₃ (210 mg, 2 mmol) were taken up in THF/H₂O (4/1, 15 ml) and stirred at 65 °C under N₂ for 19 h. The solution was partitioned between EtOAc and H₂O, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over 5 Na₂SO₄. Filtration and concentration gave a dark brown oil. Purification via flash chromatography (4/1 hexanes/Et₂O, SiO₂) gave 356 mg (100 %) of the desired product as a yellow oil.
- 2) A solution of the product in step 1 (340 mg, 0.64 mmol) and Pd(OH)₂ on carbon (300 mg, 20 wt % Pd (dry basis), 50 wt % H₂O) were taken up in 10 CH₃OH (35 ml) and shaken in a Parr apparatus under H₂ (50 psi) for 18 h. The mixture was filtered and concentrated to obtain 341 mg (100 %) of the product, (\pm)-1, as a colorless foam.
- 3) The amine (\pm)-1 was resolved via chiral HPLC separation. The conditions are as follows: CHIRALCEL® OD™ (5 cm x 30 cm); Hexane/ 15 isopropyl alcohol/diethylamine 75/25/0.05) at 25° C; 254 nm detection. The retention times for peak 1, (+)-enantiomer, and peak 2, (-)-enantiomer were 3.8 and 4.9 minutes, respectively [CHIRALCEL® OD™ (hexane/ethanol/diethylamine 90/10/0.1) 25° C at 254 nm]. Peak 1 and peak 2 are the first and second eluting peaks from the column, respectively. The enantiomers 20 (I and II) were deprotected (CH₂Cl₂/TFA), and the free amine was coupled to the 2,6-dimethylbenzoic acid using the conditions described in example 11, steps 7 and 8. The hydrochloride salts were obtained by taking the free base up in EtOAc and triturating with 1 M HCl in Et₂O.
- Data for the above compounds, 14A and 14B, and for additional 25 compounds made in a similar manner, are given in the following table. In each case, the enantiomer designator I is derived from (+)-1 and the enantiomer designated II is derived from (-)-1.



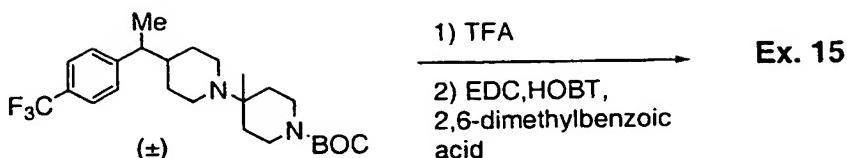
Ex.	Ar	Enantiomer	m.p. (HCl)	HRMS	
				calc	found
14A		I	185-190	565.3042	565.3050

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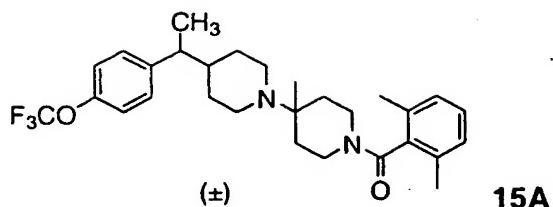
14B		II	175-180	565.3042	565.3050
14C		I	168-174	567.2947	567.2951
14D		II	170-175	567.2947	567.2957
14E		I	195-201	582.2944	582.2944
14F		II	180-185	582.2944	582.2958
14G		II	214-218	581.2991	581.2984
14H		II	145-151	658.3257	658.3251
14I		II	193-198	615.3010	615.3016
14J		II	195-200	651.3522	651.3526

Example 15

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- 1) The dibromo-olefin (3.55 g, 10 mmol) and TFA (10 ml) were taken up in CH_2Cl_2 and stirred at 25 °C for 20 h. The solution was concentrated. The residue was partitioned between CH_2Cl_2 and 1 N NaOH. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4). Filtration and concentration gave the 2.4 g (94 %) of the free piperidine as a colorless oil. The free piperidine (2.41 g, 9.45 mmol) was treated sequentially with (a) N-Boc-4-piperidone/Ti(O*i*Pr)₄, and (b) Et₂AlCN, to give the cyano-amine as described in Step 5 of Example 11.
- 5) 2) The product of Step 1 and MeMgBr (16 ml, 3.0 M in Et₂O) were taken up in THF (30 ml) and stirred at 25 °C for 19 h. The solution was quenched with 1 N NaOH and EtOAc. The mixture was filtered (Celite). The aqueous layer was extracted with EtOAc, the combined EtOAc layers were washed with brine and dried (Na_2SO_4). Filtration and concentration gave a yellow oil. Purification via flash chromatography (6/1 hexanes/EtOAc, SiO₂) gave 2.54 g (69 % from the free piperidine) of the vinyl bromide as a solid. m.p. (free base) 85-90 °C. HRMS (MH⁺) calcd. for C₁₈H₃₂O₂N₂Br, 387.1647; Found, 387.1638.
- 10) 3) The product of Step 2 (200 mg, 0.52 mmol), 4-CF₃C₆H₄B(OH)₂ (344 mg, 1.8 mmol), PdCl₂(PPh₃)₂ (36 mg, 0.052 mmol), and Na₂CO₃ (165 mg, 1.56 mmol) were taken up in THF/H₂O (4/1, 10 ml) and heated at 75 °C (oil bath) for 21 hours. The solution was partitioned between EtOAc and H₂O. The aqueous layer was extracted with EtOAc, the combined EtOAc layers were washed with brine and dried (Na_2SO_4). Filtration and concentration gave a yellow oil. Purification via flash chromatography (3/1 to 1/1 hexanes/EtOAc, SiO₂) gave 210 mg (89 %) of the phenyl substituted olefin as an oil. HRMS (MH⁺) calcd. for C₂₅H₃₆O₂N₂F₃, 453.2729; Found, 453.2728.
- 15) 4) The product of Step 3 was hydrogenated as described in Step 3 of Example 11. The reduced product was deprotected and coupled to 2,6-dimethyl benzoic acid as described in Example 11, steps 7- 8 to give the title compound as a yellow oil (37 mg, 55%). m.p. (HCl salt) 130-140 °C. HRMS (MH⁺) calcd. for C₂₉H₃₈ON₂F₃, 487.2936; Found, 487.2928.
- 20) Using a similar procedure, the following compound was prepared:



m.p. (HCl salt) 135-145°C. HRMS (MH⁺) calcd. for C₂₉H₃₈O₂N₂F₃, 503.2885; Found, 503.2896.

- 5 The following assays can be used to determine the CCR5 inhibitory and antagonistic activity of the compounds of the invention.

CCR5 Membrane Binding Assay:

A high throughput screen utilizing a CCR5 membrane binding assay identifies inhibitors of RANTES binding. This assay utilizes membranes 10 prepared from NIH 3T3 cells expressing the human CCR5 chemokine receptor which have the ability to bind to RANTES, a natural ligand for the receptor. Using a 96-well plate format, membrane preparations are incubated with ¹²⁵I-RANTES in the presence or absence of compound for one hour. Compounds are serially diluted over a wide range of 0.001ug/ml to 1 ug/ml and tested in 15 triplicates. Reaction cocktails are harvested through glass fiber filters, and washed thoroughly. Total counts for replicates are averaged and data reported as the concentration required to inhibit 50 percent of total ¹²⁵I-RANTES binding. Compounds with potent activity in the membrane binding assay are further characterized in secondary cell-based HIV-1 entry and 20 replication assays.

HIV-1 Entry Assay:

Replication defective HIV-1 reporter virions are generated by cotransfection of a plasmid encoding the NL4-3 strain of HIV-1 (which has been modified by mutation of the envelope gene and introduction of a 25 luciferase reporter plasmid) along with a plasmid encoding one of several HIV-1 envelope genes as described by Connor et al, *Virology*, **206** (1995), p. 935-944. Following transfection of the two plasmids by calcium phosphate precipitation, the viral supernatants are harvested on day 3 and a functional viral titer determined. These stocks are then used to infect U87 cells stably 30 expressing CD4 and the chemokine receptor CCR5 which have been preincubated with or without test compound. Infections are carried out for 2 hours at 37 °C, the cells washed and media replaced with fresh media containing compound. The cells are incubated for 3 days, lysed and luciferase

activity determined. Results are reported as the concentration of compound required to inhibit 50% of the luciferase activity in the control cultures.

HIV-1 Replication Assay:

- This assay uses primary peripheral blood mononuclear cells or the
5 stable U87-CCR5 cell line to determine the effect of anti-CCR5 compounds to block infection of primary HIV-1 strains. The primary lymphocytes are purified from normal healthy donors and stimulated *in vitro* with PHA and IL-2 three days prior to infection. Using a 96-well plate format, cells are pretreated with drug for 1 hour at 37 °C and subsequently infected with an M-tropic HIV-1
10 isolates. Following infection, the cells are washed to remove residual inoculum and cultured in the presence of compound for 4 days. Culture supernatants are harvested and viral replication measured by determination of viral p24 antigen concentration.

Calcium Flux Assay:

- 15 Cells expressing the HIV coreceptor CCR5 are loaded with calcium sensitive dyes prior to addition of compound or the natural CCR5 ligand. Compounds with agonist properties will induce a calcium flux signal in the cell, while CCR5 antagonists are identified as compounds which do not induce signaling by themselves but are capable of blocking signaling by the natural
20 ligand RANTES.

GTP γ S Binding Assay (secondary membrane binding assay):

- A GTP γ S binding assay measures receptor activation by CCR5 ligands. This assay measures the binding of 35 S labeled-GTP to receptor coupled G-proteins that occurs as a result of receptor activation by an appropriate ligand.
25 In this assay, the CCR5 ligand, RANTES, is incubated with membranes from CCR5 expressing cells and binding to the receptor activation (or binding) is determined by assaying for bound 35 S label. The assay quantitatively determines if compounds exhibit agonist characteristics by inducing activation of the receptor or alternatively antagonist properties by measuring inhibition of
30 RANTES binding in a competitive or non-competitive fashion.

Chemotaxis Assay:

- The chemotaxis assay is a functional assay which characterizes the agonist vs. antagonist properties of the test compounds. The assay measures the ability of a non-adherent murine cell line expressing human
35 CCR5 (BaF-550) to migrate across a membrane in response to either test compounds or natural ligands (i.e., RANTES, MIP-1 β). Cells migrate across the permeable membrane towards compounds with agonist activity. Compounds that are antagonists not only fail to induce chemotaxis, but are

also capable of inhibiting cell migration in response to known CCR5 ligands.

The role of CC chemokine receptors such as CCR-5 receptors in inflammatory conditions has been reported in such publications as

- 5 Immunology Letters, 57, (1997), 117-120 (arthritis); Clinical & Experimental Rheumatology, 17 (4) (1999), p. 419-425 (rheumatoid arthritis); Clinical & Experimental Immunology, 117 (2) (1999), p.237-243 (atopic dermatitis); International Journal of Immunopharmacology, 20 (11) (1998), p. 661-7 (psoriasis); Journal of Allergy & Clinical Immunology, 100 (6, Pt 2) (1997),
- 10 p. S52-5 (asthma); and Journal of Immunology, 159 (6) (1997), p. 2962-72 (allergies).

In the assay to determine inhibition of RANTES binding, compounds of the invention range in activity from a Ki of 0.1 to 2000 nM, with preferred compounds having a range of activity from 0.1 to 1000 nM, more preferably 15 0.1 to 500 nM, and most preferably 0.1 to 100 nM. The results for preferred and representative compounds of formulas I and II in the test to determine inhibition of RANTES binding are given in the table below. In the table, "Ex. No." stands for "Example Number" and "nM" stands for "nanomolar."

Ex. No.	Ki (nM) Inhibition of RANTES binding
1B	14
1J	1
2	9.6
2G	1.8
2S	17.9
2JJ	0.58
4B	0.5
4C	0.5
5L	7.9
5N	1.7
5O	0.4
5Z	0.3
5AB	0.1
6V	0.8
7U	62.5
9D	588

- For preparing pharmaceutical compositions from the CCR5 antagonist compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.
- Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.
- Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.
- Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.
- The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.
- Preferably the compound is administered orally.
- Preferably, the pharmaceutical preparation is in a unit dosage form.
- In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 10 mg to about 500 mg, preferably from about 25 mg to about 300 mg, more preferably from about 50 mg to about 250 mg, and most preferably from about 55 mg to about 200 mg, according
5 to the particular application.

The actual dosage of CCR5 compound employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total
10 daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the CCR5 compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician
15 considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 100 mg/day to about 300 mg/day, preferably 150 mg/day to 250 mg/day, more preferably about 200 mg/day, in two to four divided doses.

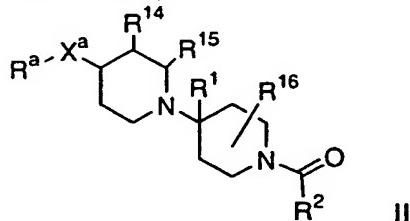
20 The doses and dosage regimens of the NRTIs, NNRTIs, PIs and other agents used in combination with the CCR5 antagonists will be determined by the attending clinician in view of the approved doses and dosage regimens in the package inserts or as set forth in the protocols, taking into consideration the age, sex and condition of the patient and the
25 severity of the condition treated.

The goal of the HIV-1 therapy of the present invention is to reduce the HIV-1-RNA viral load below the detectable limit. The "detectable limit of HIV-1-RNA" in the context of the present invention means that there are fewer than about 200 to fewer than about 50 copies of HIV-1-RNA per ml of
30 plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HIV-1-RNA is preferably measured in the present invention by the methodology of Amplicor -1 Monitor 1.5 (available from Roche Diagnositics) or of Nuclisens HIV-1 QT -1.

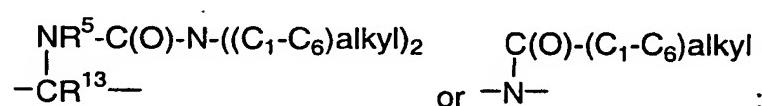
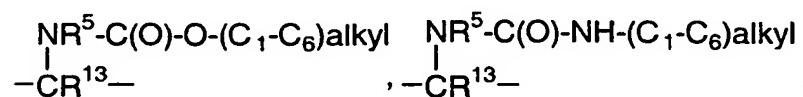
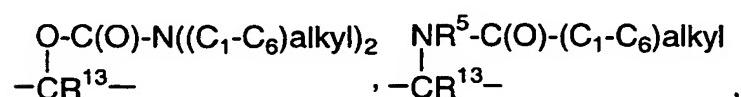
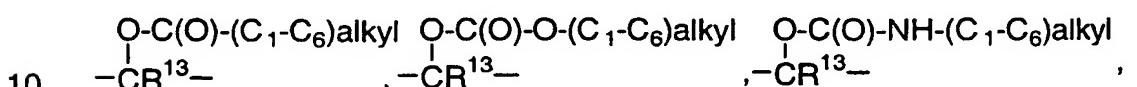
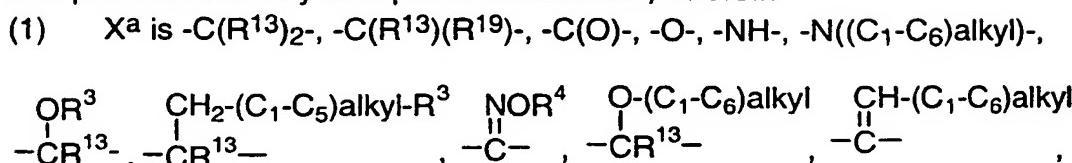
While the present invention has been described in conjunction with
35 the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound represented by the structural formula II



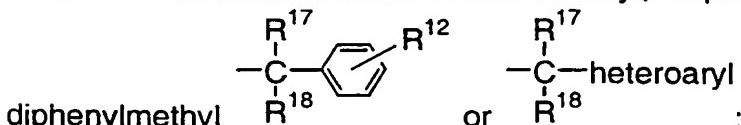
5 or a pharmaceutically acceptable salt thereof, wherein



R^a is R^{6a} -phenyl, R^{6a} -pyridyl, R^{6a} -thiophenyl or R^6 -naphthyl;

R^1 is hydrogen, $C_1\text{-C}_6$ alkyl or $C_2\text{-C}_6$ alkenyl;

20 R^2 is R^7 , R^8 , R^9 -phenyl; R^7 , R^8 , R^9 -substituted 6-membered heteroaryl; R^7 , R^8 , R^9 -substituted 6-membered heteroaryl N-oxide; R^{10} , R^{11} -substituted 5-membered heteroaryl; naphthyl; fluorenlyl;



R^3 is R^{10} -phenyl, pyridyl, pyrimidyl, pyrazinyl or thiazolyl;

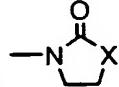
R^4 is hydrogen, $C_1\text{-C}_6$ alkyl, fluoro- $C_1\text{-C}_6$ alkyl, cyclopropylmethyl,

25 $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{-O-(C}_1\text{-C}_6\text{)alkyl}$, $-\text{CH}_2\text{C(O)-O-(C}_1\text{-C}_6\text{)alkyl}$,
 $-\text{CH}_2\text{C(O)NH}_2$, $-\text{CH}_2\text{C(O)-NH(C}_1\text{-C}_6\text{)alkyl}$ or $-\text{CH}_2\text{C(O)-N}((\text{C}_1\text{-C}_6)\text{alkyl})_2$;

R^5 and R^{11} are independently selected from the group consisting of hydrogen and $(C_1\text{-C}_6)$ -alkyl;

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R^{6a} is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, $-CF_3$, CF_3O- , $-CN$, $-CF_3SO_2-$, R^{12} -phenyl,



$-NHCOCF_3$, 5-membered heteroaryl and $-N-\text{cyclic ring}-X$, wherein X is $-O-$, $-NH-$ or $-N(CH_3)-$;

5 R^6 is independently selected from the group consisting of R^{6a} and CH_3SO_2- ;

R^7 and R^8 are independently selected from the group consisting of (C_1-C_6)alkyl, halogen, $-NR^{20}R^{21}$, $-OH$, $-CF_3$, $-OCH_3$, $-O$ -acyl, and $-OCF_3$;

R^9 is R^7 , hydrogen, phenyl, $-NO_2$, $-CN$, $-CH_2F$, $-CHF_2$, $-CHO$,

10 $-CH=NOR^{20}$, pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl, $-N(R^{20})CONR^{21}R^{22}$, $-NHCONH(\text{chloro-}(C_1-C_6)\text{alkyl})$, $-NHCONH((C_3-C_{10})\text{cycloalkyl}(C_1-C_6)\text{alkyl})$, $-NHCO(C_1-C_6)\text{alkyl}$, $-NHCOCF_3$, $-NHSO_2N((C_1-C_6)\text{alkyl})_2$, $-NHSO_2(C_1-C_6)\text{alkyl}$, $-N(SO_2CF_3)_2$, $-NHCO_2(C_1-C_6)\text{alkyl}$, $C_3-C_{10}\text{cycloalkyl}$, $-SR^{23}$, $-SOR^{23}$, $-SO_2R^{23}$, $-SO_2NH(C_1-C_6\text{ alkyl})$, $-OSO_2(C_1-C_6)\text{alkyl}$, $-OSO_2CF_3$, hydroxy(C_1-C_6)alkyl, $-CON R^{20}R^{21}$, $-CON(CH_2CH_2-O-CH_3)_2$,

15 $-OCONH(C_1-C_6)\text{alkyl}$, $-CO_2R^{20}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;

R^{10} is (C_1-C_6) alkyl, $-NH_2$ or R^{12} -phenyl;

20 R^{12} is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, $-CF_3$, $-CO_2R_{20}$, $-CN$, (C_1-C_6)alkoxy and halogen;

R^{13} , R^{14} , R^{15} and R^{16} are independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl;

25 R^{17} and R^{18} are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R^{17} and R^{18} together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R^{19} is R^6 -phenyl, R^6 -heteroaryl, R^6 -naphthyl, C_3-C_{10} cycloalkyl, (C_3-C_{10})cycloalkyl(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl;

30 R^{20} , R^{21} and R^{22} are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R^{23} is C_1-C_6 alkyl or phenyl; or

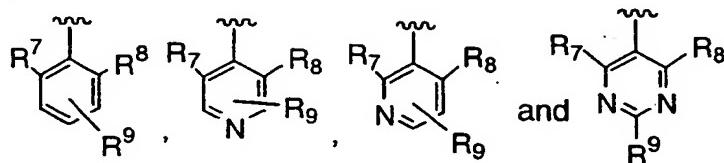
(2):

X^a is $-C(R^{13})(R^{19})-$, $-C(O)-$, $-O-$, $-NH-$, $-N((C_1-C_6)\text{alkyl})-$,

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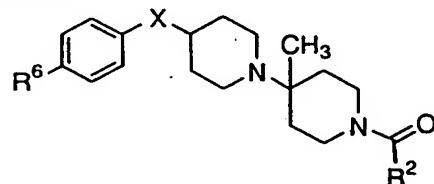
- $\begin{array}{c} \text{OR}^3 \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{CH}_2\text{-}(\text{C}_1\text{-}\text{C}_5)\text{alkyl}-\text{R}^3 \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{NOR}^{4a} \\ || \\ -\text{C}- \end{array}$ $\begin{array}{c} \text{O-C(O)-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$
- $\begin{array}{c} \text{O-C(O)-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{O-C(O)-NH-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$
- 5 $\begin{array}{c} \text{O-C(O)-N((C}_1\text{-}\text{C}_6)\text{alkyl})_2 \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{NR}^5\text{-C(O)-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$
- $\begin{array}{c} \text{NR}^5\text{-C(O)-O-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{NR}^5\text{-C(O)-NH-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ -\text{CR}^{13}- \end{array}$
- $\begin{array}{c} \text{NR}^5\text{-C(O)-N-((C}_1\text{-}\text{C}_6)\text{alkyl})_2 \\ | \\ -\text{CR}^{13}- \end{array}$ $\begin{array}{c} \text{C(O)-(C}_1\text{-}\text{C}_6)\text{alkyl} \\ | \\ \text{or } -\text{N}- \end{array}$
- ;
- 10 R^a is R^{6b} -phenyl, R^{6b} -pyridyl or R^{6b} -thiophenyl;
 R^{4a} is fluoro- $\text{C}_1\text{-}\text{C}_6$ alkyl, cyclopropylmethyl, $-\text{CH}_2\text{CH}_2\text{OH}$,
 $-\text{CH}_2\text{CH}_2\text{-O-(C}_1\text{-}\text{C}_6)\text{alkyl}$, $-\text{CH}_2\text{C(O)-O-(C}_1\text{-}\text{C}_6)\text{alkyl}$, $-\text{CH}_2\text{C(O)NH}_2$, $-\text{CH}_2\text{C(O)-NH-(C}_1\text{-}\text{C}_6)\text{alkyl}$ or $-\text{CH}_2\text{C(O)-N((C}_1\text{-}\text{C}_6)\text{alkyl})_2$;
 R^{6b} is $\text{CH}_3\text{SO}_2\text{-}$; and
- 15 $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^5, \text{R}^{14}, \text{R}^{15}, \text{R}^{16}$ and R^{19} are as defined in (1).
2. The compound of claim 1 wherein R^a is .
3. The compound of claim 1, formula II(1), wherein X^a is $-\text{CHOR}^3$,
20 $-\text{C(R}^{13})(\text{R}^{19})-$ or $-\text{C}(=\text{NOR}^{4a})-$.
4. The compound of claim 3 wherein R^3 is pyridyl, R^4 is $(\text{C}_1\text{-}\text{C}_6)$ alkyl, or
 R^{13} is hydrogen and R^{19} is R^6 -phenyl.
- 25 5. The compound of claim 1, formula II(2), wherein X^a is $-\text{CHOR}^3$,
 $-\text{C(R}^{13})(\text{R}^{19})-$ or $-\text{C}(=\text{NOR}^{4a})-$.
6. The compound of claim 5 wherein R^3 is pyridyl, R^{4a} is
 cyclopropylmethyl or trifluoroethyl, or R^{13} is hydrogen and R^{19} is R^6 -phenyl.
30 7. The compound of claim 1 wherein R^2 is $\text{R}^7, \text{R}^8, \text{R}^9$ -phenyl; $\text{R}^7, \text{R}^8,$
 R^9 -pyridyl or an N-oxide thereof; or $\text{R}^7, \text{R}^8, \text{R}^9$ -pyrimidyl.

8. The compound of claim 7 wherein R² is selected from the group consisting of



5 wherein R⁷ and R⁸ are selected from the group consisting of (C₁-C₆)alkyl, halogen, and -NH₂, and R⁹ is hydrogen.

9. A compound of claim 1 selected from the group consisting of those represented by the formula



10

wherein R⁶, X and R² are as defined in the following table:

R ⁶	X	R ²
Br	OCH ₂ CH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCOCH ₂ CH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCOOCH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCONHCH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	O-C(=O)cyclopentyl -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCOOC ₂ H ₅ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCOCH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCO(CH ₂) ₂ CH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃
Br	OCONHCH ₂ CH ₃ -CH-	H ₃ C ~~~ H ₃ C-CH=CH-CH ₃

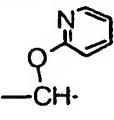
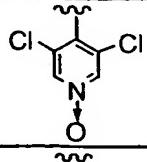
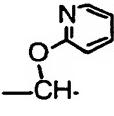
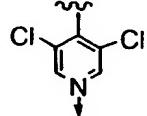
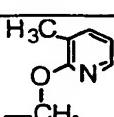
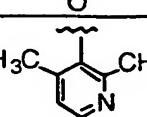
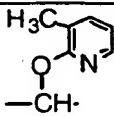
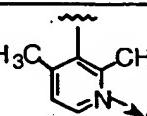
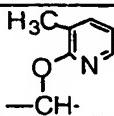
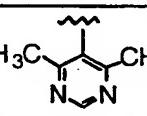
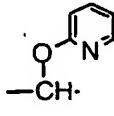
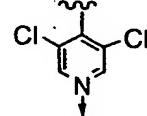
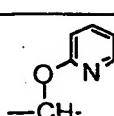
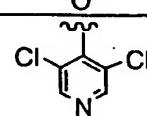
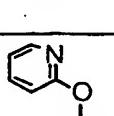
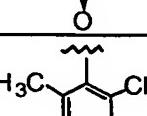
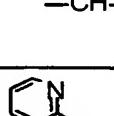
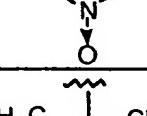
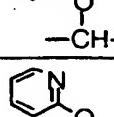
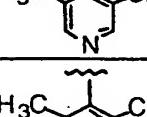
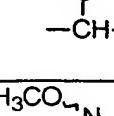
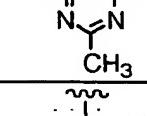
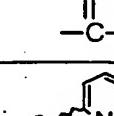
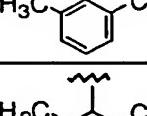
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Br		
Br		
CH ₃ SO ₂ ⁻		
Br		
H ₃ CSO ₂ ⁻		
H ₃ CSO ₂ ⁻		
F ₃ C-		
H ₃ CSO ₂ ⁻		
H ₃ CSO ₂ ⁻		
F ₃ CO-		
F ₃ CO-		

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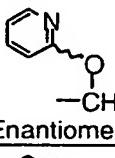
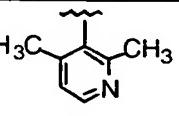
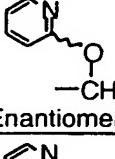
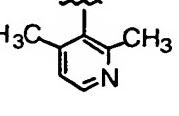
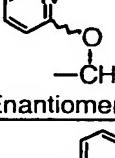
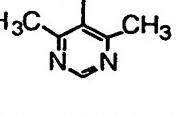
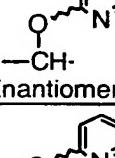
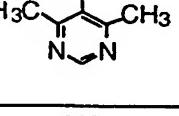
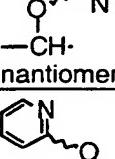
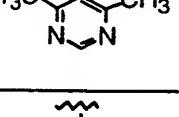
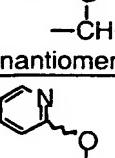
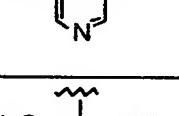
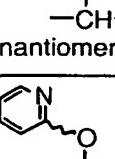
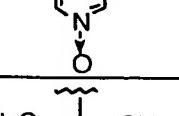
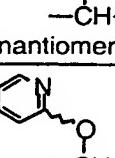
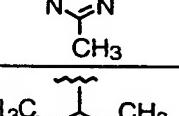
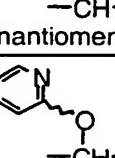
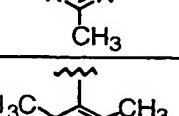
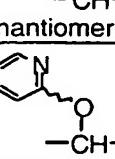
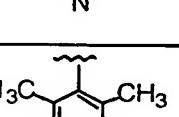
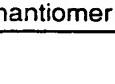
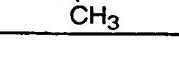
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Br		
Br		
F_3CO^-		
Br		
Br		
H_3CSO_2^-		
F_3C^-		
F_3CO^-		

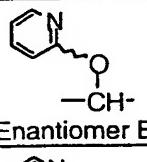
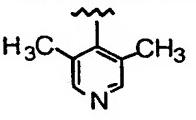
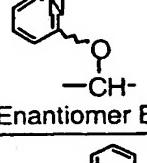
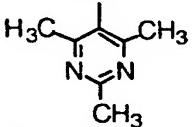
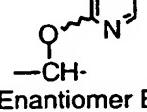
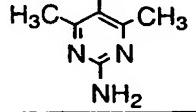
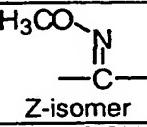
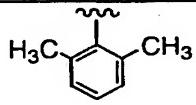
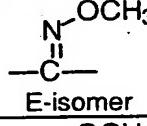
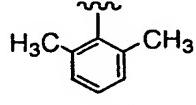
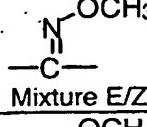
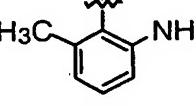
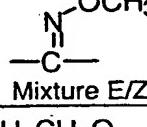
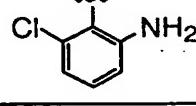
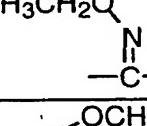
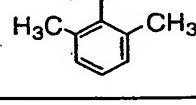
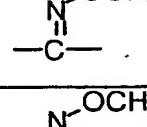
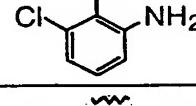
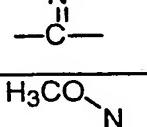
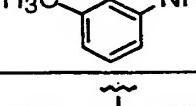
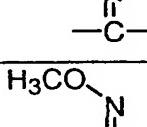
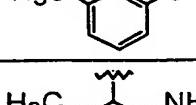
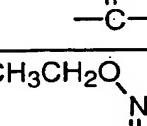
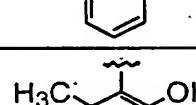
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Cl		
Br		
H_3CSO_2^-		
F_3C^-		
H_3CSO_2^-		
H_3CSO_2^-		
F_3C^-		
F		
F		
F		

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Cl		
F		
Br		
Br		
Br		
Br		
$\text{F}_3\text{C}-$		
$\text{F}_3\text{C}-$		
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F		
Br		
Br		

Enantiomer A

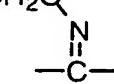
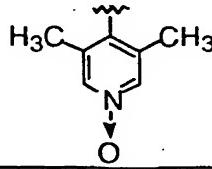
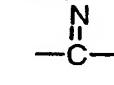
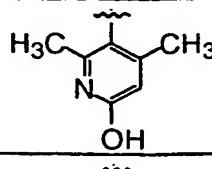
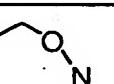
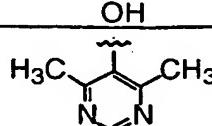
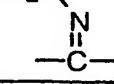
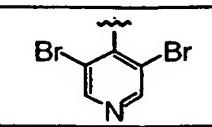
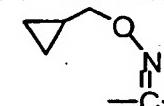
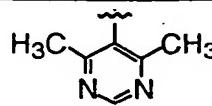
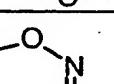
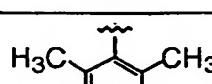
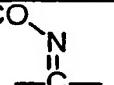
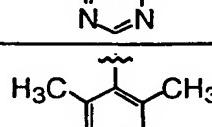
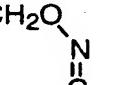
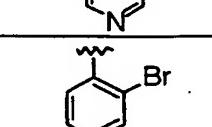
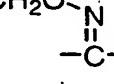
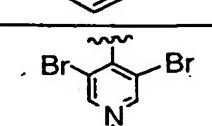
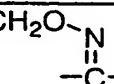
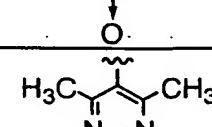
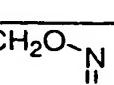
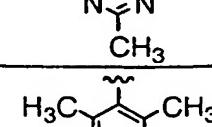
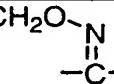
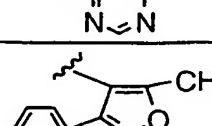
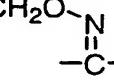
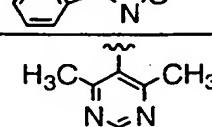
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Br	 Enantiomer B	
Br	 Enantiomer B	
F ₃ CO-	 Enantiomer A	
F ₃ CO-	 Enantiomer B	
F ₃ CO-	 Enantiomer A	
F ₃ CO-	 Enantiomer A	
F ₃ CO-	 Enantiomer A	
F ₃ CO-	 Enantiomer B	
Cl	 Enantiomer A	
Cl	 Enantiomer A	

Cl	 Enantiomer B	
Cl	 Enantiomer B	
F ₃ CO-	 Enantiomer B	
Br	 Z-isomer	
Br	 E-isomer	
Br	 Mixture E/Z	
Br	 Mixture E/Z	
Br	 CH ₃ CH ₂ O-	
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Br	 H ₃ CO-	
Br	 CH ₃ CH ₂ O-	

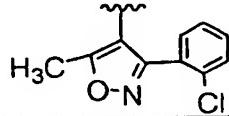
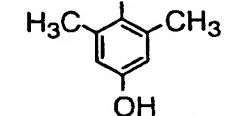
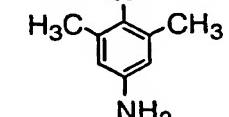
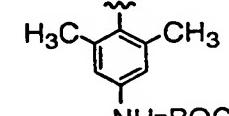
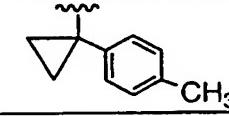
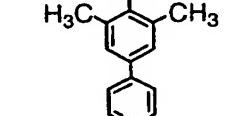
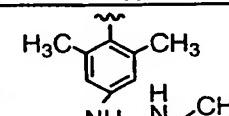
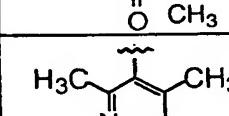
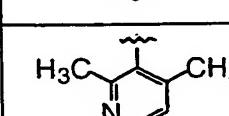
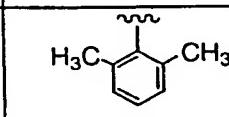
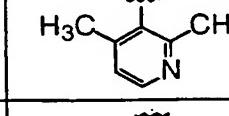
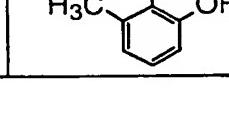
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Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{OCH}_2\text{CH}_3-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CF}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CF}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$	
Br	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	

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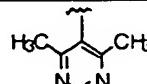
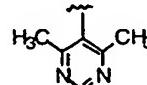
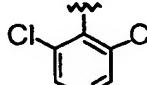
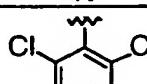
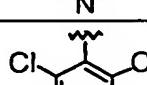
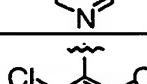
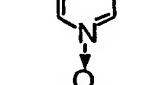
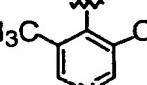
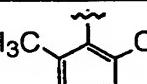
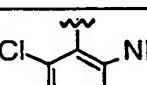
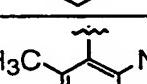
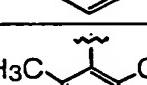
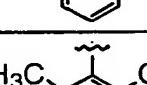
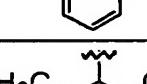
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Br	$\text{CH}_3\text{CH}_2\text{Q}$ 	
Br	$\text{H}_3\text{C}-\text{CH}_2-\text{O}-\text{N}=\text{C}-$ 	
Br	$\text{CH}_3\text{CH}_2\text{Q}$ 	
Br		
Br	$\text{H}_3\text{C}-\text{CH}_2-\text{O}-\text{N}=\text{C}-$ 	
Br	$\text{H}_3\text{CO}-\text{N}=\text{C}-$ 	
Br	$\text{CH}_3\text{CH}_2\text{Q}$ 	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$ 	
Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$ 	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$ 	
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Br	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$ 	

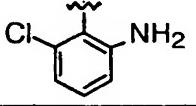
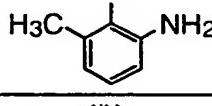
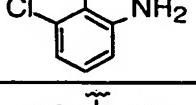
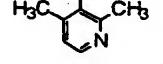
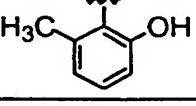
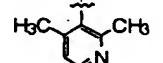
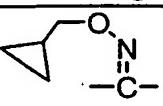
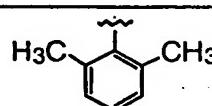
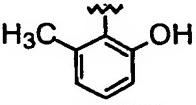
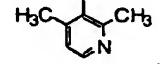
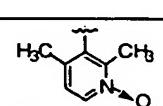
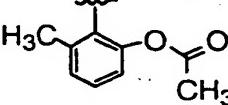
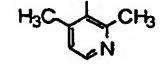
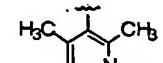
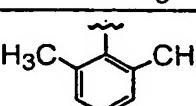
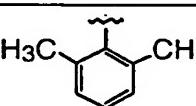
- 90 -

Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Br	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{H}_3\text{CO}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$ Z-isomer	
$\text{F}_3\text{CO}-$	$\text{OCH}_3-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$ E-isomer	
Br	$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{N}}{\equiv}}-\text{C}-$	
Br	$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{N}}{\equiv}}-\text{C}-$	
Br	$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{N}}{\equiv}}-\text{C}-$	

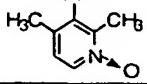
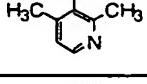
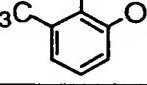
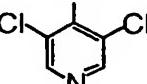
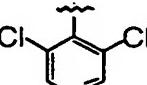
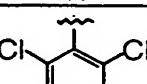
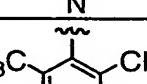
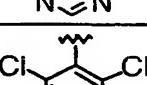
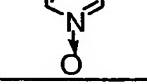
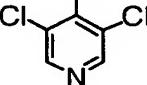
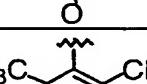
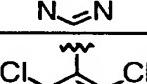
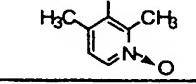
Br	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br		
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{F}_3\text{CCH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$		
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	

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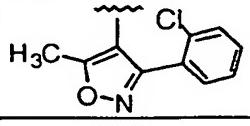
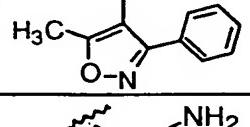
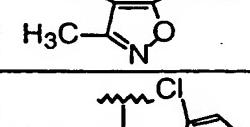
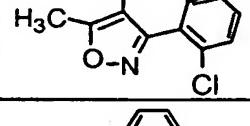
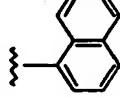
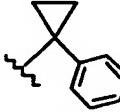
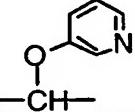
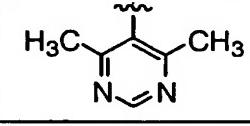
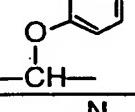
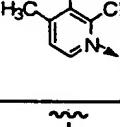
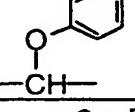
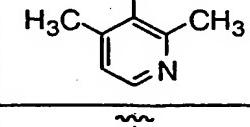
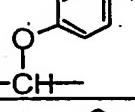
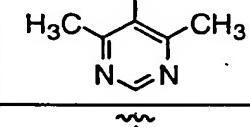
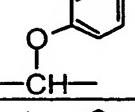
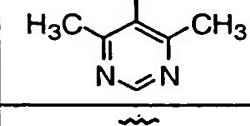
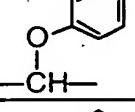
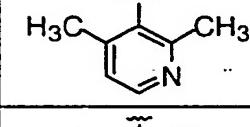
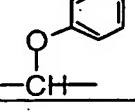
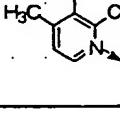
Cl	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
Cl	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\overset{\text{N}}{\underset{\text{C}}{\equiv}}-\text{C}-$ E isomer	

$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$		
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$ E isomer	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$ E isomer	
$\text{F}_3\text{CO}-$	$\text{H}_3\text{CO}(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	

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$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$		
$\text{F}_3\text{CO}-$		
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{CO}-$	$\text{CH}_3(\text{CH}_2)_2\text{O}-\text{N}=\text{C}-$	
Br	$\text{CH}_3\text{O}-\text{N}=\text{C}-$	
$\text{F}_3\text{C}-$	$\text{CH}_3\text{CH}_2\text{O}-\text{N}=\text{C}-$	

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Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br	-CH ₂ -	
Br		
CH ₃ SO ₂ ⁻		
Br		
Br		
F		
F		
F		

- 96 -

Br		
Cl		
F ₃ C-		
CH ₃ SO ₂ -		
CH ₃ SO ₂ -		
F ₃ CO-		
F ₃ CO-		
CH ₃ SO ₂ -		
CH ₃ SO ₂ -		
F ₃ C-		
F ₃ CO-		
F ₃ CO-		
F ₃ C-		

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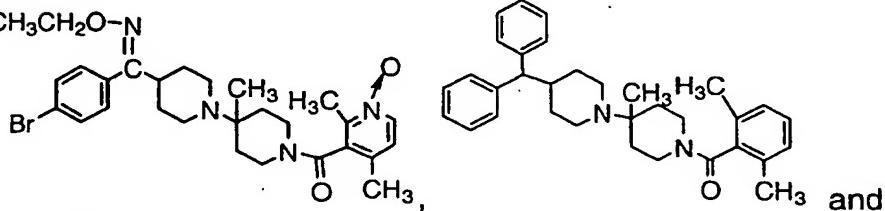
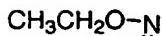
H		
F ₃ CO-		

Enantiomer II

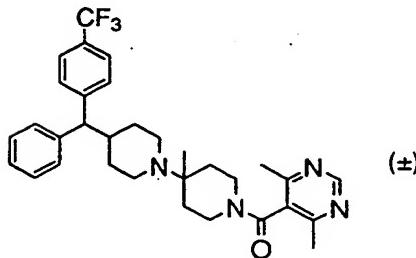
Enantiomer II

Enantiomer II

10. A compound selected from the group consisting of



and

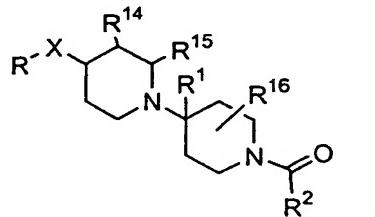


5

11. A pharmaceutical composition for the treatment of Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis, comprising an effective amount of a CCR5 antagonist of claim 1 in combination with a pharmaceutically acceptable carrier.
- 10

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12. The use of a compound of claim 1 for the preparation of a medicament for treating Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis.
13. The use of a compound of claim 1 for the preparation of a medicament for combined use with one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus,
- 10 14. The use of claim 13 wherein the antiviral agent is selected from the group consisting of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.
- 15 15. The use of a compound of claim 1 for the preparation of a medicament for combined use with one or more agents for treating solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis.
- 20 16. The use of a CCR5 antagonist of formula I for the preparation of a medicament for treating Human Immunodeficiency Virus, solid organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies or multiple sclerosis, wherein the CCR5 antagonist is represented by the
- 25 structural formula I:

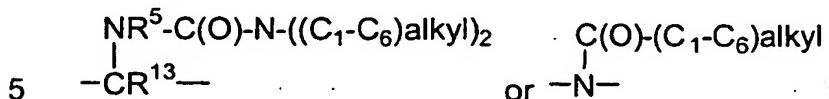
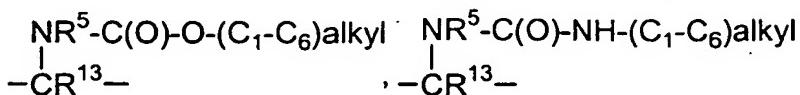
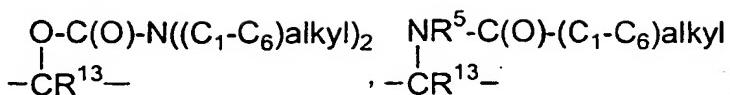


or a pharmaceutically acceptable salt thereof, wherein

X is $-\text{C}(\text{R}^{13})_2-$, $-\text{C}(\text{R}^{13})(\text{R}^{19})-$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{NH}-$, $-\text{N}((\text{C}_1\text{-}\text{C}_6)\text{alkyl})-$,

30 $\begin{array}{ccccc} \text{OR}^3 & \text{CH}_2\text{-(C}_1\text{-C}_5\text{)alkyl-R}^3 & \text{NOR}^4 & \text{O-(C}_1\text{-C}_6\text{)alkyl} & \text{CH-(C}_1\text{-C}_6\text{)alkyl} \\ | & | & || & | & | \\ -\text{CR}^{13}- & -\text{CR}^{13}- & -\text{C}- & -\text{CR}^{13}- & -\text{C}- \\ , & , & , & , & , \\ \text{O-C(O)-(C}_1\text{-C}_6\text{)alkyl} & \text{O-C(O)-O-(C}_1\text{-C}_6\text{)alkyl} & \text{O-C(O)-NH-(C}_1\text{-C}_6\text{)alkyl} & & \\ -\text{CR}^{13}- & ,-\text{CR}^{13}- & ,-\text{CR}^{13}- & & \end{array}$

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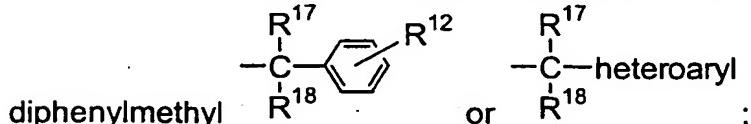


R is R⁶-phenyl, R⁶-pyridyl, R⁶-thiophenyl or R⁶-naphthyl;

R¹ is hydrogen, C₁-C₆ alkyl or C₂-C₆ alkenyl;

R² is R⁷, R⁸, R⁹-phenyl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl; R⁷, R⁸, R⁹-substituted 6-membered heteroaryl N-oxide;

10 R¹⁰, R¹¹-substituted 5-membered heteroaryl; naphthyl; fluorenyl;



R³ is R⁶-phenyl, R⁶-heteroaryl or R⁶-naphthyl;

R⁴ is hydrogen, C₁-C₆ alkyl, fluoro-C₁-C₆ alkyl, cyclopropylmethyl,

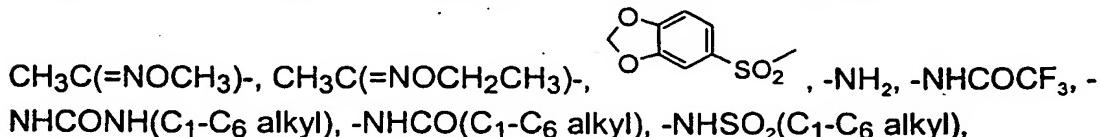
-CH₂CH₂OH, -CH₂CH₂-O-(C₁-C₆)alkyl, -CH₂C(O)-O-(C₁-C₆)alkyl,

15 -CH₂C(O)NH₂, -CH₂C(O)-NH(C₁-C₆)alkyl or -CH₂C(O)-N((C₁-C₆)alkyl)₂;

R⁵ and R¹¹ are independently selected from the group consisting of hydrogen and (C₁-C₆)-alkyl;

R⁶ is 1 to 3 substituents independently selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -CF₃, CF₃O-,

20 CH₃C(O)-, -CN, CH₃SO₂-, CF₃SO₂-, R¹⁴-phenyl, R¹⁴-benzyl,



5-membered heteroaryl and $\begin{array}{c} \text{O} \\ \parallel \\ \text{N-X} \end{array}$, wherein X is -O-, -NH- or -N(CH₃)-;

25 R⁷ and R⁸ are independently selected from the group consisting of (C₁-C₆)alkyl, halogen, -NR²⁰R²¹, -OH, -CF₃, -OCH₃, -O-acyl, and -OCF₃;

R⁹ is R⁷, hydrogen, phenyl, -NO₂, -CN, -CH₂F, -CHF₂, -CHO, -CH=NOR²⁰,

pyridyl, pyridyl N-oxide, pyrimidinyl, pyrazinyl,

-N(R²⁰)CONR²¹R²², -NHCONH(chloro-(C₁-C₆)alkyl), -NHCONH((C₃-C₁₀)

cycloalkyl(C₁-C₆)alkyl), -NHCO(C₁-C₆)alkyl, -NHCOCF₃, -NSO₂N((C₁-

30 C₆)alkyl)₂, -NSO₂(C₁-C₆)alkyl, -N(SO₂CF₃)₂, -NHCO₂(C₁-C₆)alkyl, C₃-C₁₀

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cycloalkyl, $-SR^{23}$, $-SOR^{23}$, $-SO_2R^{23}$, $-SO_2NH(C_1-C_6\text{ alkyl})$, $-OSO_2(C_1-C_6)\text{alkyl}$, $-OSO_2CF_3$, hydroxy(C_1-C_6)alkyl, $-CON R^{20}R^{21}$, $-CON(CH_2CH_2-O-CH_3)_2$, $-OCONH(C_1-C_6)\text{alkyl}$, $-CO_2R^{20}$, $-Si(CH_3)_3$ or $-B(OC(CH_3)_2)_2$;
 R¹⁰ is (C_1-C_6)alkyl, $-NH_2$ or R¹²-phenyl;

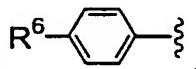
5 R¹² is 1 to 3 substituents independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, $-CF_3$, $-CO_2R_{20}$, $-CN$, (C_1-C_6)alkoxy and halogen;

R¹³, R¹⁴, R¹⁵ and R¹⁶ are independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl;

10 R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or R¹⁷ and R¹⁸ together are a C_2-C_5 alkylene group and with the carbon to which they are attached form a spiro ring of 3 to 6 carbon atoms;

R¹⁹ is R⁶-phenyl, R⁶-heteroaryl, R⁶-naphthyl, C_3-C_{10} cycloalkyl, (C_3-C_{10})cycloalkyl(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl;
 15 R²⁰, R²¹ and R²² are independently selected from the group consisting of H and C_1-C_6 alkyl; and

R²³ is C_1-C_6 alkyl or phenyl.

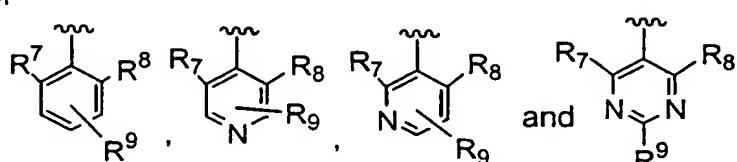
20 17. The use of claim 16 wherein R is .

18. The use of claim 16 wherein X is $-CHOR^3$, $-C(R^{13})(R^{19})-$ or $-C(=NOR^4)-$.

25 19. The use of claim 18 wherein R³ is pyridyl, R⁴ is (C_1-C_6)alkyl, or R¹³ is hydrogen and R¹⁹ is R⁶-phenyl.

20. The use of claim 16 wherein R² is R⁷, R⁸, R⁹-phenyl, R⁷, R⁸, R⁹-pyridyl or an N-oxide thereof, or R⁷, R⁸, R⁹-pyrimidyl.

30 21. The use of claim 20 wherein R² is selected from the group consisting of



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wherein R⁷ and R⁸ are selected from the group consisting of (C₁-C₆)alkyl, halogen, and -NH₂, and R⁹ is hydrogen.

22. The use of claim 16 for the treatment of Human Immunodeficiency Virus, further comprising one or more antiviral or other agents useful in the treatment of Human Immunodeficiency Virus.

23. The use of claim 22 wherein the antiviral agent is selected from the group consisting of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

24. The use of claim 16 for the treatment of solid organ transplant rejection, graft v. host disease, inflammatory bowel disease, rheumatoid arthritis or multiple sclerosis, further comprising one or more other agents useful in the treatment of said diseases.

25. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat Human Immunodeficiency Virus which comprises in one container a pharmaceutical composition comprising an effective amount of a CCR5 antagonist of claim 16 in a pharmaceutically acceptable carrier, and in separate containers, one or more pharmaceutical composition comprising an effective amount of a antiviral or other agent useful in the treatment of Human Immunodeficiency Virus in a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11633

A. CLASSIFICATION OF SUBJECT MATTER				
IPC 7 C07D211/58 C07D417/14 C07D401/14 C07D413/14 A61K31/4468 A61K31/4523 A61P31/12 A61P19/00				
According to International Patent Classification (IPC) or to both national classification and IPC				
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IPC 7 C07D A61K A61P				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)				
EPO-Internal, CHEM ABS Data, WPI Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages			Relevant to claim No.
X	WO 98 05292 A (SCHERING CORP) 12 February 1998 (1998-02-12) claims 1,13; examples & US 5 889 006 A 30 March 1999 (1999-03-30) cited in the application			1,2,25
X	WO 98 06697 A (SCHERING CORP) 19 February 1998 (1998-02-19) claims 1,11; examples			1,2,25
X	WO 98 01425 A (SCHERING CORP) 15 January 1998 (1998-01-15) claims 1,11; examples			1,2,25
				-/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.		
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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